# The American Journal of Cardiology®

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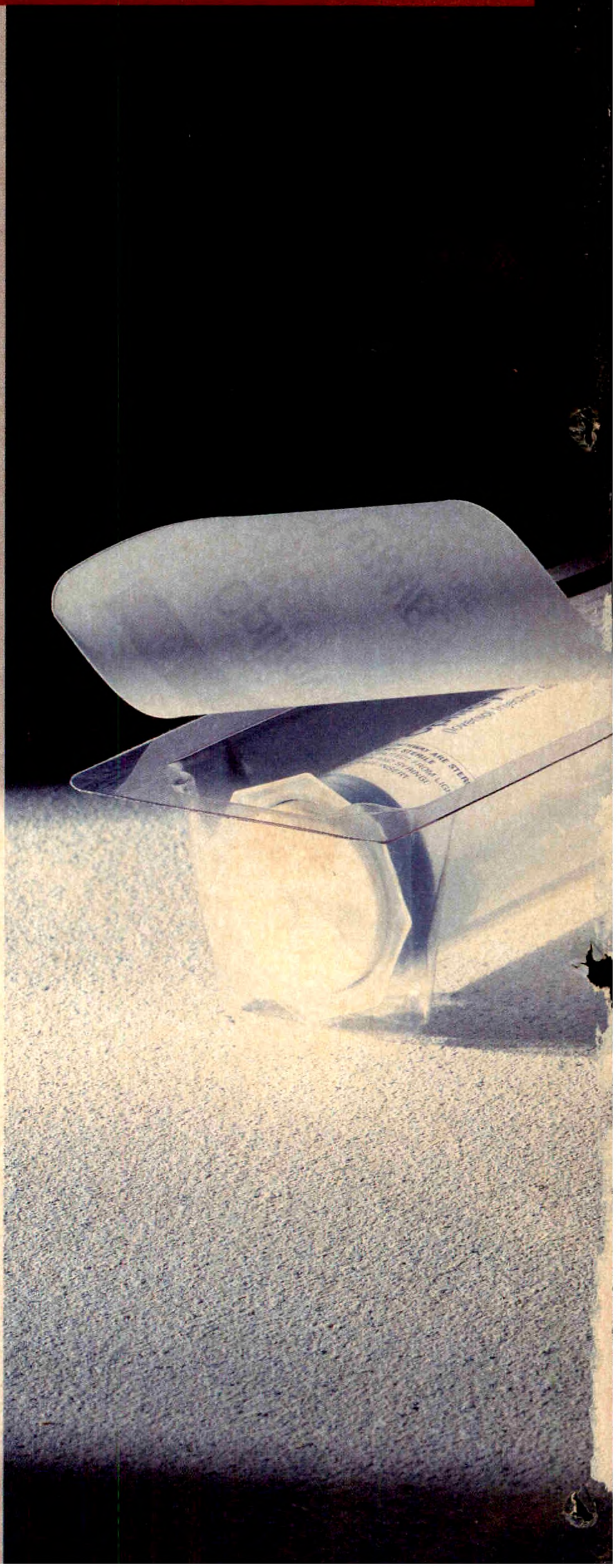

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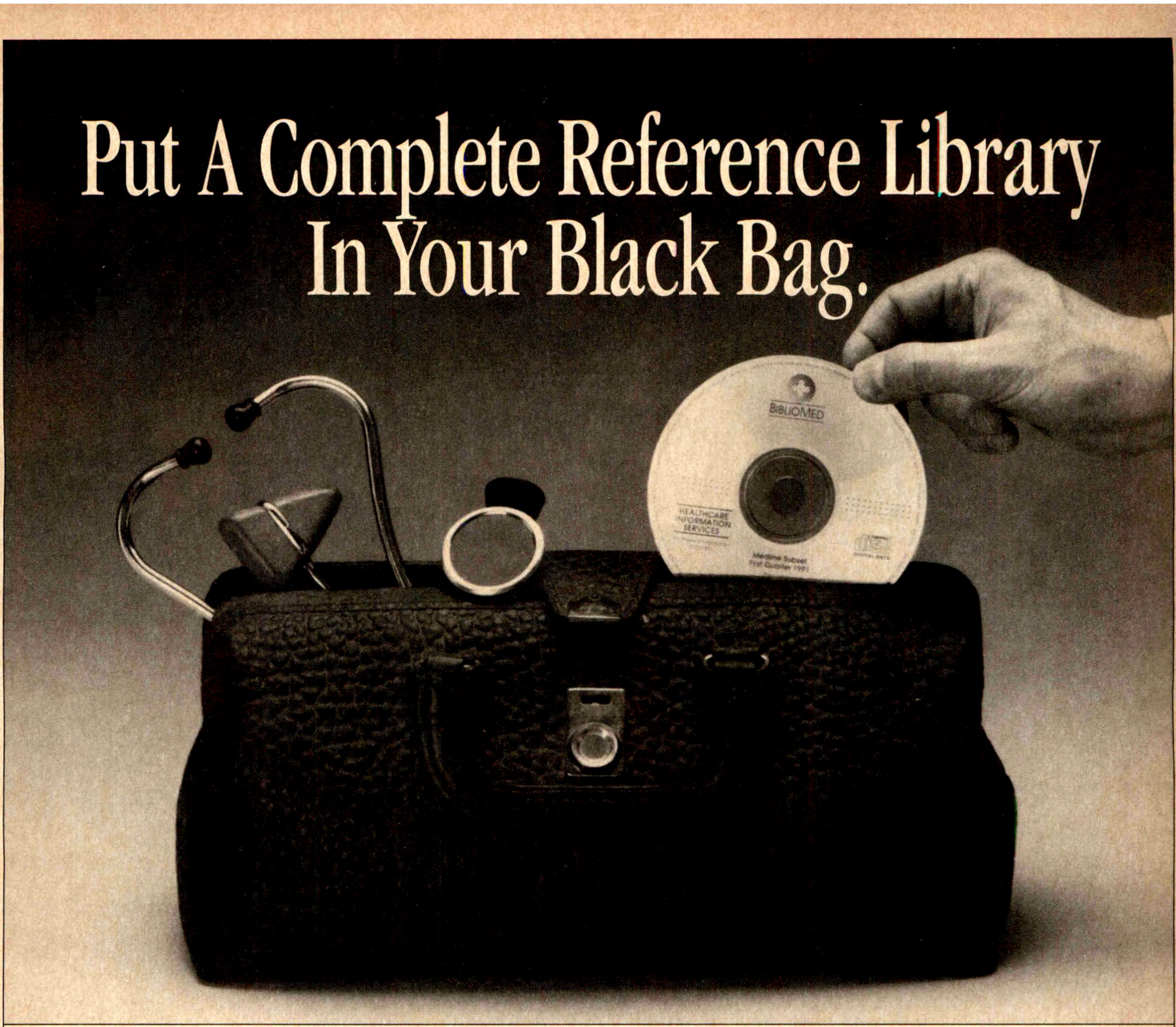
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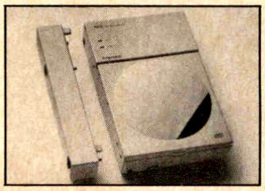

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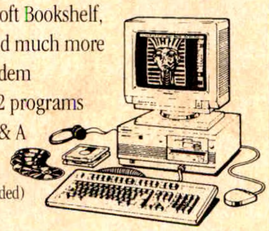

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## CORONARY ARTERY DISEASE

**1263**

### Acute and Chronic Antianginal Efficacy of Continuous Twenty-Four-Hour Application of Transdermal Nitroglycerin

Steering Committee, Transdermal Nitroglycerin Cooperative Study

This rigorously controlled double-blind trial in 562 patients with chronic angina pectoris who were randomized to placebo or doses of nitroglycerin from 15 to 105 mg/24 hours was designed to evaluate the development of tolerance to continuously applied transdermal nitroglycerin using exercise treadmill testing as the end point. Acutely, exercise performance improved 4 hours after initial application of 15 mg/24 hour patches (+34 seconds versus placebo; $p < 0.05$). This difference was no longer evident 24 hours after the first application or for the remaining 8 weeks of the trial despite increases in the transdermal dose up to 105 mg/24 hours. A partial tolerance to a sublingual nitroglycerin exercise challenge was also seen, with the highest doses leading to the greatest attenuation. Although there were no overall differences between groups in daily anginal frequency, a post-hoc analysis revealed that in a subset of the most symptomatic (>7 attacks per week at baseline) patients, angina was reduced by 6 to 7 attacks per week in those receiving active patches versus a decrease of 2 attacks per week in patients receiving placebo patches ($p < 0.05$). This study clearly demonstrated that tolerance to exercise treadmill effects of continuously applied transdermal nitroglycerin occurs within 24 hours after initial patch application, and that tolerance is not overcome by increasing the dose.

**1274**

### Digoxin-Induced Vasoconstriction of Normal and Atherosclerotic Epicardial Coronary Arteries

Ciro Indolfi, Federico Piscione, Enrico Russolillo, Bruno Villari, Paolo Golino, Vittorio Ambrosini, Mario Condorelli, and Massimo Chiariello

The effects of digoxin infusion and sublingual administration of isosorbide dinitrate on large coronary arteries were investigated in patients with angiographically normal coronary arteries (group I) and in patients with atherosclerotic lesions (group II). In group I, 10 minutes after the end of digoxin infusion, cross-sectional area decreased from 7.7 ± 4.1 to 6.0 ± 2.2 $mm^2$, and after 20 minutes to 5.6 ± 2.6 $mm^2$ ($p < 0.05$). In group II, minimal stenosis diameter decreased significantly 20 minutes after digoxin infusion from 1.6 ± 0.5 to 1.4 ± 0.5 mm ($p < 0.05$). Thus, bolus infusion

Continued on page A16

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of digoxin induced vasoconstriction of normal epicardial coronary arteries and reduced minimal stenosis diameter in patients with coronary artery disease. Digoxin-induced vasoconstriction was not mediated by an $\alpha$-adrenergic mechanism and was reverted by sublingual administration of isosorbide dinitrate.

## 1279

## Usefulness of Ambulatory Silent Myocardial Ischemia Added to the Prognostic Value of Exercise Test Parameters in Predicting Risk of Cardiac Death in Patients with Stable Angina Pectoris and Exercise-Induced Myocardial Ischemia

Prakash C. Deedwania and Enrique V. Carbajal

The prognostic significance of ambulatory silent ischemia was prospectively evaluated and compared with several exercise test parameters in patients with stable angina pectoris and a positive exercise test. There were 86 patients (47 [group 1] without and 39 with [group 2] silent ischemia during ambulatory electrocardiographic monitoring). During follow-up (24 ± 8 months) there were 11 cardiac deaths (2 [nonsudden] in group 1 [4% mortality] and 9 [3 sudden, 6 nonsudden] in group 2 [23% mortality; $p < 0.008$]). Multivariate Cox's regression analysis revealed ambulatory silent ischemia as the most powerful predictor of cardiac mortality ($p = 0.003$). These findings reveal that presence of ambulatory silent ischemia in patients with stable angina provides significant additional prognostic information to that derived from evaluation of exercise test parameters alone.

## 1287

## Usefulness of Electrocardiographic Findings and Creatine Kinase Levels on Admission in Predicting the Accuracy of the Interval Between Onset of Chest Pain of Acute Myocardial Infarction and Initiation of Thrombolytic Therapy

Aernout M. Beek, Freek W. A. Verheugt, and Albert Meyer

To evaluate the relation of patient history to enzymes on admission and electrocardiography, 221 consecutive patients eligible for thrombolytic therapy were studied. Patients with symptoms within 6 hours ($n = 170$, early) received thrombolytic therapy, but those with symptoms after 6 hours did not ($n = 51$, late). Creatine kinase levels on admission less than twice the upper normal limit were found in 155 (91%) early patients, but, surprisingly, also in 30 (59%) late patients. By electrocardiography on admission, ST-segment elevation was significantly higher in late patients with low initial enzymes than in those with elevated initial enzymes. Concomitantly, Q waves in leads with ST-segment elevation were present in about half of the late patients with low enzymes on admission and in nearly all of those with elevated enzymes on admission. Eventually, maximal creatine kinase levels were similar in all late patients irrespective of enzyme levels on admission. Therefore, many patients with symptoms of acute myocardial infarction after 6 hours have low enzymes on admission and may still be eligible for thrombolytic therapy. Immediate enzyme testing and electrocardiography on admission may identify these patients. These data could be the basis for the improved survival reported with "late" thrombolytic therapy.

**Continued on page A19**

### 1291

## Frequency of Use of Thrombolytic Therapy in Acute Myocardial Infarction in Israel

Solomon Behar, Edward Abinader, Avi Caspi, Daniel David, Michael Flich, Yaacov Friedman, Hanoch Hod, Elieser Kaplinsky, Yehezkiel Kishon, Natalio Kristal, Shlomo Laniado, Vladimier Markiewicz, Abraham Palant, Benyamin Pelled, Leonardo Reisin, Tiberio Rosenfeld, Natan Roguin, Libi Sherf, Babeth Rabinowitz, Zwi Schlesinger, Samuel Sclarovsky, Izhar Zahavi, Monty Zion, and Uri Goldbourt

During a 1-month survey, 145 of 413 patients (35%) with acute myocardial infarction (AMI) hospitalized in 18 coronary care units in Israel were treated with thrombolytic therapy. The latter treatment was more often given to men, patients aged up to 75 years and those with a first AMI. Hospital mortality was significantly higher in patients ineligible for thrombolysis but these patients had different characteristics than the counterparts treated with a thrombolytic agent. The 2 most common reasons for ineligibility for thrombolysis were late hospital arrivals and lack of ST elevation on the admission electrocardiogram.

### 1295

## Effect of Propranolol (Long-Acting) on the Circadian Fluctuation of Tissue-Plasminogen Activator and Plasminogen Activator Inhibitor-1

Felicita Andreotti, Cornelis Kluft, Graham J. Davies, Linda G.M. Huisman, Anton C.W. de Bart, and Attilio Maseri

The incidence of myocardial infarction and inhibition of fibrinolytic activity in blood both peak in the morning. It is reported that $\beta$ blockade blunts the higher morning frequency of myocardial infarction. This study therefore investigates whether propranolol alters the circadian variation of 2 major fibrinolytic factors, tissue-type plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1). Blood was taken every 3 hours for 24 hours in 13 healthy volunteers: 7 taking long-acting propranolol, 160 mg/day for 14 days, and 6 taking no medications. The plasma activity and antigen levels of t-PA and PAI-1 showed a significant circadian fluctuation in both groups. Peak and nadir values, 24-hour mean, amplitude of fluctuation, and time of peak and nadir were not significantly different between groups. Thus, propranolol does not affect the circadian rhythm of t-PA and PAI-1. The reported alteration in the circadian pattern of onset of myocardial infarction by $\beta$ blockers does not appear to be mediated by effects on the fibrinolytic system.

### 1300

## Specificity and Sensitivity of QRS Criteria for Diagnosis of Single and Multiple Myocardial Infarcts

Olle Pahlm, Wesley K. Haisty, Jr., Nancy B. Wagner, James E. Pope, and Galen S. Wagner

A subset of 3 criteria from the complete Selvester scoring system has been proposed earlier for electrocardiographic screening of healed myocardial infarcts. In the present study an automated version of these criteria was applied to 1,344 electrocardiograms from normal subjects, 706 from subjects with single infarcts, and 131 from subjects with combined anterior and inferior infarcts. Overall specificity was only 86%, whereas overall sensitivity was 77%. Differences in waveform measurements between the manual and computer methods accounted for a large part of the deterioration of specificity in this study compared with previously published results. One of the screening criteria (R $\geq$40 ms in $V_1$) may possibly be eliminated to augment specificity; this can be done with only minor loss of sensitivity. Computer application of the screening criteria requires altered criteria limits in comparison with those used in manual application. Probably sex- and age-dependent criteria limits should be used.

**1305**

### Intracoronary Ultrasound Evaluation of Interventional Technologies

Charles J. Davidson, Khalid H. Sheikh, Katherine B. Kisslo, Harry R. Phillips, Robert H. Peter, Victor S. Behar, Yihong Kong, Mitchell Krucoff, E. Magnus Ohman, James E. Tcheng, and Richard S. Stack

The feasibility and applicability of intravascular ultrasound (IVUS) were evaluated in 70 patients undergoing coronary interventional procedures. Coronary interventions included 45 percutaneous transluminal coronary angioplasties, 9 excimer lasers, 11 directional coronary atherectomies, 3 rotational atherectomies and 2 stents. IVUS provided supplemental morphologic data not identified with angiography including plaque composition, plaque topography and vessel dissection. Postprocedure minimal lumen diameter and cross-sectional area measured by IVUS were larger and poorly correlated with angiography; $r = 0.28$, standard error of the estimate = 0.52; $r = 0$, standard error of the estimate = 1.0 $cm^2$, respectively. Thus, ultrasound-determined postinterventional luminal dimensions are discordant with quantitative angiography. IVUS is more sensitive than angiography when assessing postinterventional lesion characteristics including vessel dissection and plaque morphology. Catheter-based ultrasound is a useful adjunct in contrast to angiography when evaluating and comparing the therapeutic impact of conventional percutaneous transluminal coronary angioplasty with new technologies.

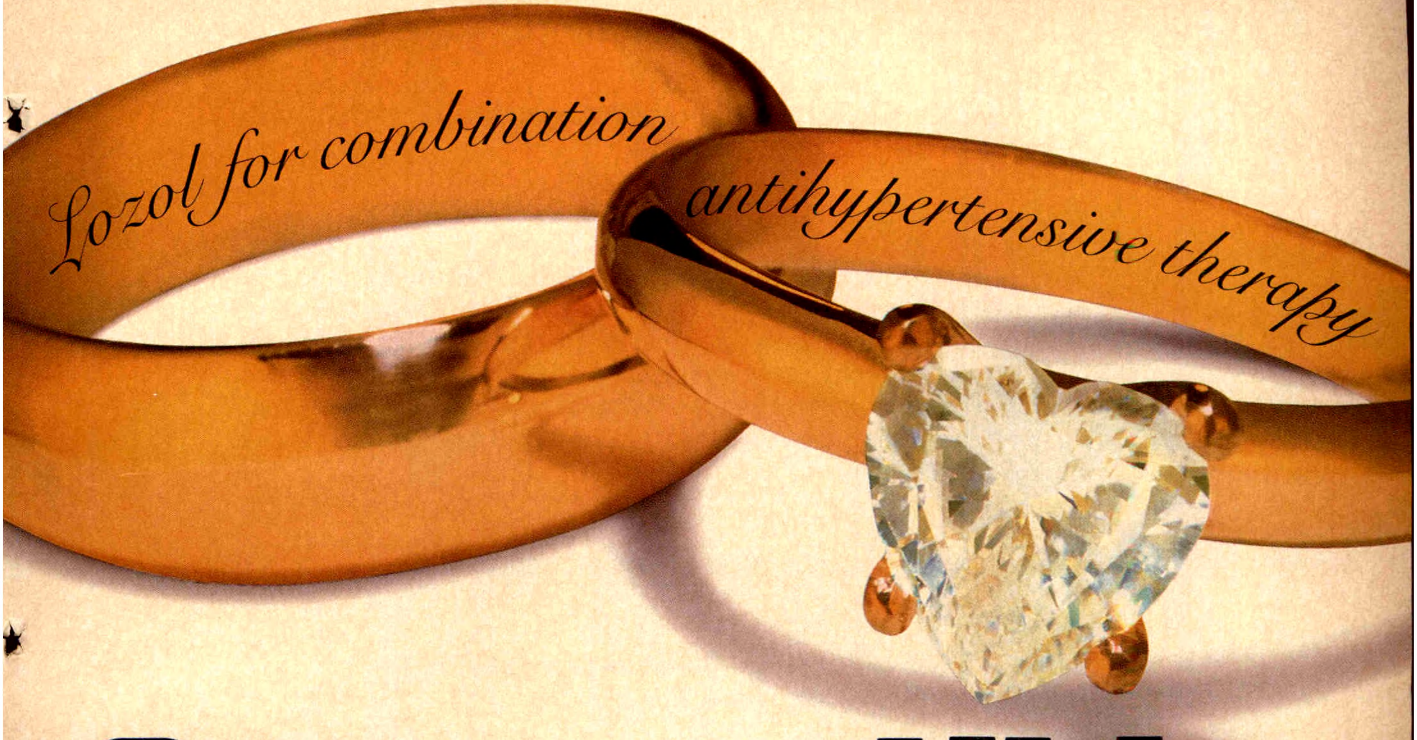
**1310**

### Usefulness of Morphologic Parameters in Predicting the Outcome of Coronary Excimer Laser Angioplasty

Andreas Baumbach, Karl K. Haase, and Karl R. Karsch

Lesion morphology and the outcome of coronary excimer laser angioplasty were analyzed in 148 consecutive interventions. Failure of laser angioplasty is increased in totally occluded vessels and in target vessels with prestenotic vessel tortuosity. Laser angioplasty is therefore limited by reduced catheter flexibility and the requirement of guidewire support. Statistical analysis of the morphologic parameters in successful stand-alone laser interventions compared with combined or unsuccessful interventions revealed no significant difference. Thus, once the catheter has reached the target, lesion morphology appears to be of minor importance for the outcome of coronary excimer laser angioplasty.

**Continued on page A24**



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### 1316

### Early and Late Results of Coronary Angioplasty and Bypass in Octogenarians

Matthew J. Mick, Conrad Simpfendorfer, Anita Z. Arnold, Marion Piedmonte, and Bruce W. Lytle

To identify the best treatment strategy for octogenarians with symptomatic coronary artery disease, the early and late results of 195 octogenarians undergoing percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were compared. Early and late results for this nonrandomized group were similar. Octogenarians with severe symptomatic coronary artery disease should be considered for revascularization despite advanced age.

## ARRHYTHMIAS AND CONDUCTION DISTURBANCES

### 1321

### Effects of Increased Heart Rate and Sympathetic Tone on Intraventricular Electrogram Morphology

Cynthia J. Finelli, Lorenzo A. DiCarlo, Janice M. Jenkins, Stuart A. Winston, and Pai-Chi Li

Effects of increased heart rate and sympathetic tone on the intraventricular electrogram appearance were evaluated. Intraventricular electrogram morphology, as assessed by correlation waveform analysis, remained stable in 36 of 39 patients (92%), whereas electrogram area and peak-to-peak amplitude fluctuated during accelerated heart rate caused by atrial overdrive pacing and infusion of sympathetic amines. However, overall morphology remained stable. Thus, template-based algorithms for recognition of ventricular tachycardia should remain robust in the face of physiologically accelerated heart rate.

### 1329

### Role of Concealed and Supernormal Conductions During Atrial Fibrillation in the Preexcitation Syndrome

Peng-Sheng Chen and Eric N. Prystowsky

The hypothesis that retrograde concealed and anterograde supernormal conductions over the accessory pathway are determinants of accessory pathway conduction during atrial fibrillation was prospectively tested. In 15 patients with both preexcited and normal QRS complexes, after normal complexes the cycle length preceding the first preexcited QRS complex was 389 ± 69 ms, which was longer than the average cycle length of consecutive preexcited complexes (325 ± 55 ms; $p = 0.001$). In 2 patients with multiple accessory pathways, 1 accessory pathway conducted only after short preceding cycle lengths (355 to 360 and 181 to 185 ms). In conclusion, retrograde concealed conduction to the accessory pathway and anterograde supernormal accessory pathway conduction are factors that, in part, determine accessory pathway conduction during atrial fibrillation.

Continued on page A26

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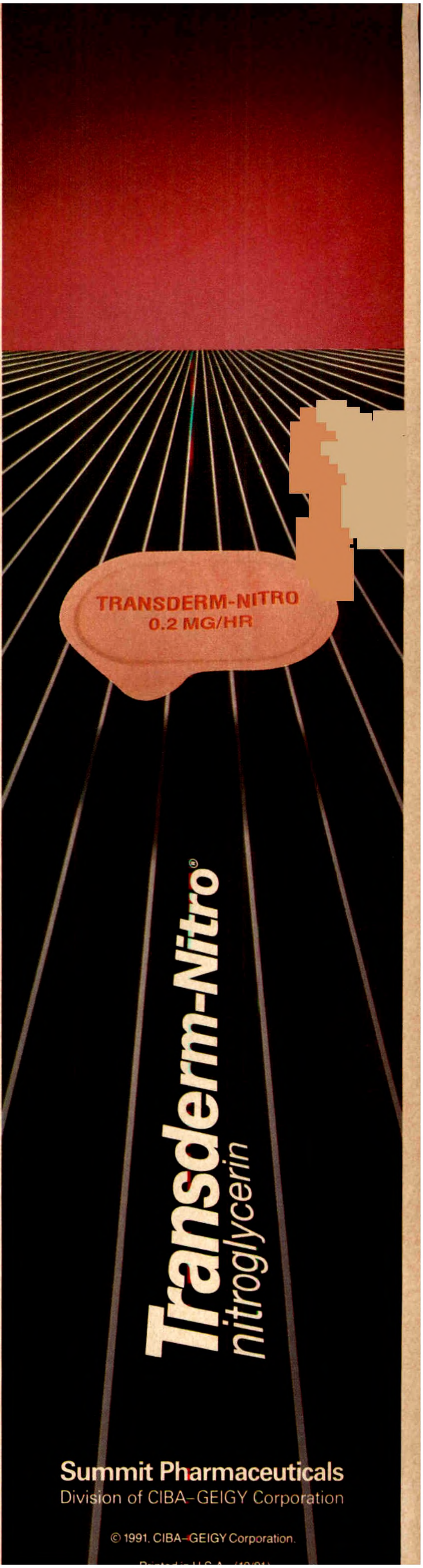

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### 1335

## Superior Vena Cava Flow and Tricuspid Anular Motion After Cardioversion of Atrial Fibrillation, and Role of Right Atrial Relaxation on Systolic Venous Return

Hiroshi Ochi, Shiro Izumi, Rinji Murakami, Toshio Shimada, Shigefumi Morioka, and Katsutoshi Moriyama

To determine whether atrial relaxation or systolic descent of the tricuspid anulus is the predominant factor determining systolic venous return, 22 patients with atrial fibrillation were studied. Superior vena cava (SVC) flow and tricuspid anular motion were measured using pulsed Doppler or M-mode echocardiography. Serial examinations of SVC flow and tricuspid anular motion were performed before and after cardioversion. Both total excursion of the tricuspid anulus and SVC flow were also examined in relation to the ratio of the preceding to the pre-preceding RR interval (R2/R1). Systolic forward flow of SVC correlated with the ratio of late diastolic to total excursion of the tricuspid anulus (i.e., atrial function), but not with total excursion. Total excursion correlated with R2/R1, but systolic forward flow of SVC did not. These results indicate that atrial relaxation rather than descent of the tricuspid anulus was the predominant factor determining systolic venous return.

### 1340

## Operative Mortality with Implantation of the Automatic Cardioverter-Defibrillator

Robert D. Mosteller, Michael H. Lehmann, Andra C. Thomas, Kenneth Jackson, and Participating Investigators

In 939 consecutive patients undergoing initial implantation of an automatic implantable cardioverter-defibrillator at 15 hospitals, 29 patients (3.1%) died during the first 30 days after surgery. A reference group of 219 survivors (with known ejection fractions) had clinical characteristics similar to that of the mortality group, except for a significantly higher ejection fraction (34 ± 15 vs 26 ± 10%, respectively, $p < 0.001$). Perioperative deaths were classified as: sudden in 7 (24%), tachyarrhythmic/nonsudden in 5 (17%), cardiac nonarrhythmic in 9 (31%), and noncardiac in 8 (28%). Sustained ventricular tachycardia or fibrillation accounted for all 9 in-hospital sudden and tachyarrhythmic/nonsudden deaths; 5 (56%) of these fatalities occurred in the setting of initially deactivated devices. Additional factors that may have played a role in sudden or tachyarrhythmic/nonsudden death included acute myocardial ischemia or infarction in 2 (17%), "device proarrhythmia" in 3 (25%), and lack of defibrillation threshold testing in 3 (25%). These findings have relevance to patient selection and intra- and postoperative management practices related to automatic cardioverter-defibrillator implantation.

Continued on page A32

***unknown):*** Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

**OVERDOSAGE** Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazeprilat can be removed from the body by dialysis, but this intervention should rarely, if ever, be required.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

**DOSAGE AND ADMINISTRATION** The recommended initial dose for patients not receiving a diuretic is 10 mg once-a-day. The usual maintenance dosage range is 20-40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2-6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response an increase in dosage or divided administration should be considered. If blood pressure is not controlled with Lotensin alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of Lotensin with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Lotensin. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with Lotensin (see WARNINGS). Then, if blood pressure is not controlled with Lotensin alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg Lotensin should be used to avoid excessive hypotension.

**Dosage Adjustment in Renal Impairment**

For patients with a creatinine clearance <30 mL/min/1.73 $m^2$ (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg Lotensin once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg.

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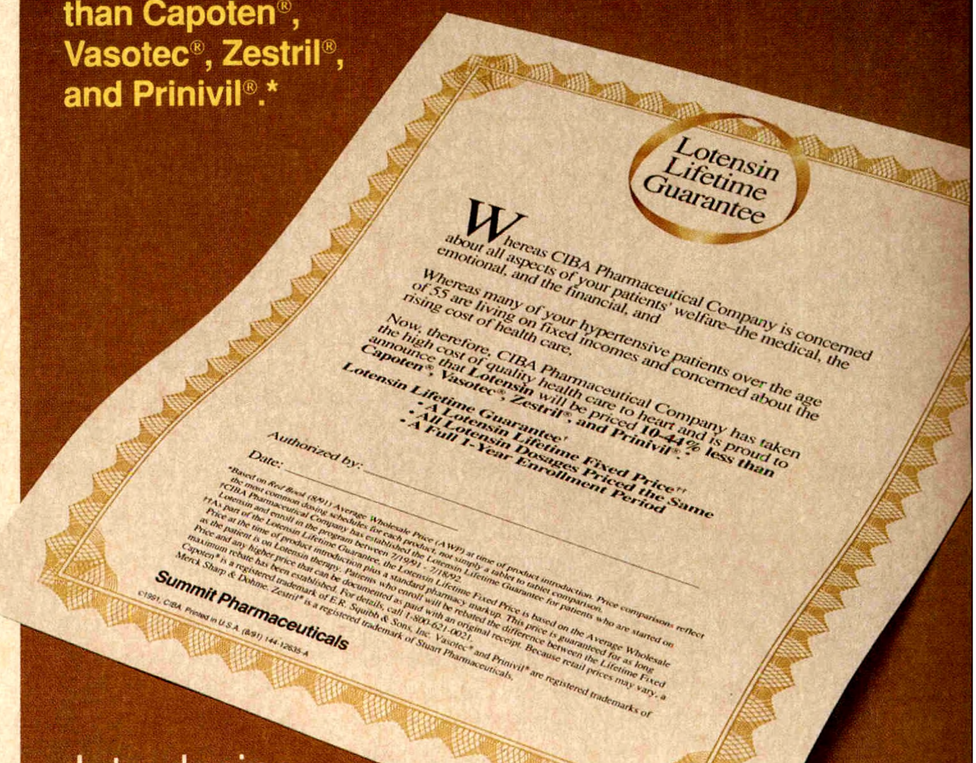

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## SYSTEMIC HYPERTENSION

### 1346

### Hemodynamic Comparison of Two Nifedipine Formulations in Patients with Essential Hypertension

Edward D. Frohlich, Mario J. McLoughlin, Christoph J. Losem, Reinhard Ketelhut, and Franz H. Messerli

The hemodynamic and humoral effects and trough-to-peak 24-hour blood pressure responses of 2 nifedipine formulations, capsules and continuous-release formulation tablets, were evaluated in 10 patients with mild to moderate essential hypertension. Both formulations similarly reduced mean arterial pressure from 120 ± 3 to 107 ± 2 and 105 ± 2 mm Hg ($p < 0.005$) and total peripheral resistance from 65 ± 9 to 47 ± 4 and 45 ± 3 ($p < 0.05$) $U/m^2$, respectively. Renal, splanchnic and total forearm blood flows were maintained or even increased slightly, associated with reductions in regional vascular resistances. Decreases in renal and forearm resistances were significant ($p < 0.05$) with capsules, but the decrease was only significant in renal resistance with the tablets. Intravascular volume did not expand with pressure reduction. The long-acting formulation nifedipine provided a better control pressure reduction (66%) than the capsules (44%), particularly with early morning readings.

### 1351

### Effect of Nifedipine Tablets on Ambulatory Blood Pressure in Patients Aged <60 and >65 Years with Systemic Hypertension

Iwao Kuwajima, Yasuko Suzuki, Tatsuo Shimosawa, Kuniaki Otsuka, Hiroshi Kawamura, and Kizuko Kuramoto

To assess the effect of age on the pattern of circadian blood pressure after administration of nifedipine tablets, ambulatory blood pressure (BP) after low (10 mg, twice daily) and high doses (20 mg, twice daily) of nifedipine were measured over a 24-hour period in 10 elderly and 8 young hypertensive patients. In both groups, whole-day averages of systolic and diastolic BP had significant decreases from the control to the low-dose period. After the high-dose period, only the elderly group had a significant further reduction in systolic BP, whereas no further reduction was observed in the young group. Separate analysis into daytime and nighttime values revealed that further decrease in systolic BP after the high-dose period in the elderly group was a reflection of nighttime decline.

### 1357

### Effects of Hydrochlorothiazide, Diltiazem and Enalapril on Mononuclear Cell Sodium and Magnesium Levels in Systemic Hypertension

Abraham S. Abraham, Barry A. Brooks, Yisrael Grafstein, Ester Barchilon, Nafez Nubani, Uri Eylath, and Ovadia Shemesh

Treatment with hydrochlorothiazide, enalapril or diltiazem resulted in a reduction in blood pressure in 56 elderly patients with mild to moderate hypertension. Serum potassium decreased by 17% ($p < 0.05$) in patients who received hydrochlorothiazide, but returned to normal when enalapril

**Continued on page A35**

was substituted. Hydrochlorothiazide also produced a 23% reduction in mononuclear cell sodium content at 4 weeks ($p < 0.01$), with a further 15% decrease at 12 weeks ($p < 0.05$). Mononuclear cell potassium and magnesium also decreased at 12 weeks (by 18 and 16%, respectively; $p < 0.05$). All these effects were reversed when enalapril was substituted. Similar trends were seen with diltiazem, which were again reversed by enalapril. There was no relation between changes in mononuclear cell sodium or other cation content and changes in blood pressure.

**1362**

### Response to Mental and Physical Stress Before and During Adrenoreceptor Blocker and Angiotensin-Converting Enzyme Inhibitor Treatment in Essential Hypertension

Esther Paran, Lily Neumann, Natalio Cristal, and David T. Lowenthal

The effects of mental, static and dynamic stresses on physiologic parameters before and after $\beta$-blocker and angiotensin-converting enzyme inhibitor treatment were examined. Mental stress induced similar elevation in systolic and diastolic blood pressures (BPs) with and without $\beta$-blocker treatment. During angiotensin-converting enzyme inhibitor treatment, the change in systolic BP was significantly greater. Skin temperature and galvanic skin resistance significantly decreased with mental stress. This decrease was attenuated by angiotensin-converting enzyme inhibitor. After handgrip exercise, increases in systolic and diastolic BPs and heart rate were similar before and after $\beta$-blocker treatment, whereas the angiotensin-converting enzyme inhibitor induced small but significantly fewer changes in diastolic BP and heart rate. Treadmill exercise induced similar changes in systolic and diastolic BPs with both treatments compared with no treatment. The angiotensin-converting enzyme inhibitor appears to provide additional protection during mental and static stressors.

## VALVULAR HEART DISEASE

**1367**

### Clinical and Anatomic Observations in Patients Having Mitral Valve Replacement for *Mitral Stenosis* and Simultaneous Tricuspid Valve Replacement

Erik A. Eways and William C. Roberts

Certain clinical and morphologic findings are described in 67 patients (aged 23 to 76 years [mean 52], 55 women [82%]) who had mitral valve replacement for mitral stenosis (with or without associated regurgitation), and simultaneous tricuspid valve replacement for pure tricuspid regurgitation (58 patients) or tricuspid stenosis (all with associated regurgitation; 9 patients). Of the 58 patients with pure tricuspid regurgitation, 21 had anatomically normal and 37 had anatomically abnormal (diffusely fibrotic leaflets) tricuspid valves. Among these 58 patients, no clinical or hemodynamic variable was useful before surgery in distinguishing the group without from that with anatomically abnormal tricuspid valves. All 9 patients with stenotic tricuspid valves had anatomically abnormal tricuspid valves. The latter group had a lower average right ventricular systolic pressure (tricuspid valve closing pressure) than those with pure tricuspid regurgitation, and none had severe pulmonary arterial hypertension (present in 20 [30%] of the 58 patients with pure tricuspid regurgitation).

## CARDIOMYOPATHY

1372

### Prognostic Features of Children with Idiopathic Dilated Cardiomyopathy

Henry B. Wiles, Patrick D. McArthur, Ashby B. Taylor, Paul C. Gillette, Derek A. Fyfe, John P. Matthews, and Leslie W. Shelton

The improved results of cardiac transplantation in children has created a greater emphasis on defining the outcome of children with idiopathic dilated cardiomyopathy. Only by knowing the outcome of this disease can patients be identified who would benefit most from this surgical intervention. This study reviewed the presenting clinical features, diagnostic evaluation and clinical outcome of 39 children with dilated cardiomyopathy. No consistent clinical feature accurately predicted the 33% who died, 42% who improved or 25% in whom idiopathic dilated cardiomyopathy resolved. The appropriate use and timing of cardiac transplantation in children with dilated cardiomyopathy remains a difficult question.

## CONGENITAL HEART DISEASE

1377

### Effect of Digoxin on Contractility and Symptoms in Infants with a Large Ventricular Septal Defect

Thomas R. Kimball, Stephen R. Daniels, Richard A. Meyer, David W. Hannon, Jason Tian, Rakesh Shukla, and David C. Schwartz

Nineteen infants with symptoms of congestive heart failure due to a large ventricular septal defect were studied to determine if digoxin improves contractility and symptoms when added to diuretics. Symptoms, signs (heart and respiratory rates, and weight gain), shortening fraction, preload, afterload and contractility were measured during each of 4 study periods: (1) before medication; (2) while on diuretics alone; (3) while on diuretics and digoxin; and (4) while on diuretics alone. When digoxin was added to diuretics, contractility was significantly greater than in control subjects. When patients were again on diuretics alone, contractility was no longer different. There was no significant improvement in symptoms and signs with diuretics alone or in combination with digoxin. It is concluded that although contractility index significantly improved in infants with a large ventricular septal defect shunt while on digoxin and diuretics compared with that in control subjects, neither medication improved symptoms significantly.

Continued on page A38

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**References:** **1.** Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol.* 1991;31:144-150. **2.** Data on file for VERELAN 240 mg, Lederle Laboratories, Pearl River, NY.

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Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

**CONTRAINDICATIONS:** Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

**WARNINGS:** Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- and third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

**PRECAUTIONS:** Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

**ADVERSE REACTIONS:** Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN *verapamil HCl sustained-release pellet-filled capsules* for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2,2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain.

**Cardiovascular:** angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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## MISCELLANEOUS

### 1383

### Age-Related Variation In Contractility Estimate in Patients ≤20 Years of Age

Thomas R. Kimball, Stephen R. Daniels, Philip Khoury, and Richard A. Meyer

To determine reproducibility and age and sex dependence of the relation of velocity of fiber shortening (VCF) to wall stress (WS), 204 children (113 boys, 91 girls) were divided into 3 groups: group 1 <6 months old (n = 27), group 2 >6 months but <3 years old (n = 38), and group 3 >3 and <20 years old (n = 139). All underwent echocardiography. In addition, 25 patients underwent serial echocardiography (n = 44). Only 1 of these 44 repeat data pairs of VCF and WS was outside the 95% confidence limits for that relation. VCF was significantly inversely and linearly related to WS in all groups (p = 0.001). There was a significant difference in the regression lines between groups. The younger groups had significantly steeper slopes and higher y-intercepts than the older group (p <0.01). There was no relation to gender. When examining contractile state in young patients, clinicians and investigators need to relate data points to the appropriate age-related regression line.

### 1388

### Sudden Unexpected Death in Persons <40 Years of Age

Yaacov Drory, Yoseph Turetz, Yehuda Hiss, Boaz Lev, Enrique Z. Fisman, Amos Pines, and Mordechai R. Kramer

Retrospective assessment of underlying causes and prodromal symptoms in sudden unexpected death in 162 subjects (aged 9 to 39 years) revealed cardiac, noncardiac and unidentifiable causes in 73, 15 and 12% of subjects, respectively. Myocarditis (22%), hypertrophic cardiomyopathy (22) and conduction system abnormalities (13) were the major causes in 32 subjects aged <20 years. Among subjects aged 20 to 29 years, there were 46 deaths (atherosclerotic coronary artery disease [24%], myocarditis [22] and hypertrophic cardiomyopathy [13]). Atherosclerotic coronary artery disease accounted for 58% and myocarditis for 11% of deaths in 84 subjects aged ≥30 years. Among noncardiac causes, intracranial hemorrhage was most frequent (5%), followed by infectious disease (4). Prodromal symptoms were reported by 54% of subjects. Sudden death during routine daily activity in 49% and sleep in 23% of subjects was related to physical exercise in 23% and emotional upset in 6%. Early recognition of prodromal symptoms could be crucial in the prevention of sudden death, specifically when exercise-related.

## EDITORIAL

### 1393

### The Mystery of Nitrate Resistance

Jonathan Abrams

Continued on page A41

## BRIEF REPORTS

**1397**

**Reproducibility and Relation to the Degree of Myocardial Ischemia of Postexercise Electrocardiographic Changes in Stable Angina Pectoris**

Giuseppe Pupita, Ornella Mattei, Domenico Mazzara, Maurizio Centanni, Gino Fabrizio Ferretti, Carla Rimatori, Paolo Dessí-Fulgheri, Paolo Russo, and Alessandro Rappelli

**1400**

**Hemodynamic Resistance to Intravenous Nitroglycerin In Severe Congestive Heart Failure And Restored Response After Diuresis**

Philip Varriale, William J. David, and Basil E. Chryssos

**CLASSIFIED ADVERTISING on pages A82, A83, A84**

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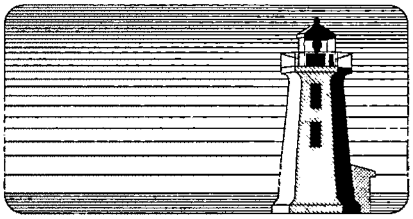

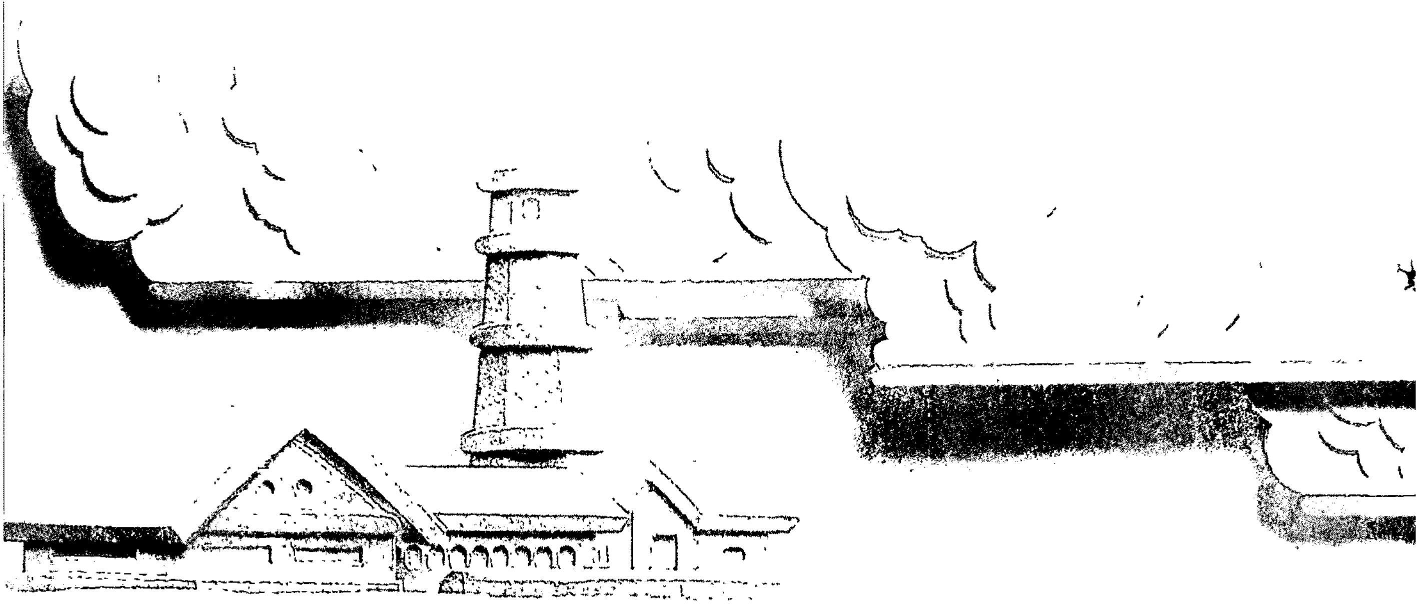

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CORONARY ARTERY DISEASE

The American Journal of Cardiology®

NOVEMBER 15, 1991, VOL. 68, NO. 13

# Acute and Chronic Antianginal Efficacy of Continuous Twenty-Four-Hour Application of Transdermal Nitroglycerin

Steering Committee, Transdermal Nitroglycerin Cooperative Study

**To resolve the controversies surrounding the antianginal use of chronic, continuous 24-hour transdermal nitroglycerin therapy, a double-blind, placebo-controlled, randomized, parallel-group study was designed. Eligible patients had chronic angina pectoris with symptom-limited, reproducible treadmill tests and were responsive to sublingual nitroglycerin (n = 562). Patients were randomly assigned to placebo or 1 of 7 doses of active treatment (15, 30, 45, 60, 75, 90 and 105 mg/24 hours). In the active drug groups, treatment was initiated with 15 mg/24 hours during the first week of double-blind dosing with subsequent weekly increases until the assigned dose was reached, after which the dose was held constant. Treadmill tests were performed 0, 4 and 24 hours after the initial double-blind patches were applied, after each titration step and after 8 weeks. At the end of double-blind therapy, a sublingual nitroglycerin exercise challenge was repeated. Exercise tolerance in patients using the active patch increased 34 seconds ($p < 0.05$) over patients taking placebo 4 hours after the initial application of double-blind therapy, but there was no statistically significant difference in exercise time between placebo and active drug groups by 24 hours after the first application or for the remaining 8 weeks of the trial. Increasing the dose did not overcome the loss of effect. A partial attenuation of the response to a sublingual nitroglycerin challenge seen on exercise tolerance testing also occurred, with patients who received the highest dose showing the greatest attenuation. There were no differences in angina frequency among the groups, although in a post hoc analysis, patients with >7 attacks per week had a reduction in anginal frequency of 6 to 7 attacks per week with active treatment versus 2 attacks per week with placebo. The study showed that (1) tolerance to the exercise effects of continuous transdermal nitroglycerin develops within 24 hours after application; and (2) increasing the dose does not overcome this tolerance. The observation that symptomatic improvement may occur in the absence of increases in exercise tolerance seems deserving of further study.**

**(Am J Cardiol 1991;68:1263–1273)**

Transdermally applied nitroglycerin systems gained wide use for the prophylactic treatment of angina pectoris after their initial marketing because they provided a convenient way of maintaining a constant serum concentration of nitroglycerin.[1] However, despite acceptance by physicians and patients,[2] concerns regarding tolerance to chronic continuous administration (24-hour application) of nitroglycerin began to emerge. Whereas several double-blind, placebo-controlled trials documented acute and chronic antianginal efficacy as measured by either exercise tolerance[3–7] or symptomatology,[3,5,8–12] other investigations[13–19] failed to demonstrate sustained activity after the first 24 hours of initial patch application. One reason for these discordant findings may have been that most of these studies were of relatively small sample sizes with insufficient power to draw definitive conclu-

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From Searle Research and Development, Skokie, Illinois; the Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey; and the Schering-Plough Corporation, Kenilworth, New Jersey. The work described was funded by CIBA-GEIGY Pharmaceuticals Division, G.D. Searle & Co. and Key Pharmaceuticals. Manuscript received December 31, 1990; revised manuscript received and accepted July 8, 1991.

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sions. In an effort to resolve this controversy, a study of adequate statistical power was designed to determine whether chronic continuous transdermal nitroglycerin was effective and how it compared with acute administration; to see whether a dose-response relation existed with transdermal patches; and to learn whether doses larger than those currently used in clinical practice were required for efficacy.

## METHODS

**Study protocol:** The study was a randomized, double-blind, placebo-controlled, multicenter, parallel group, dose-response trial. Patients were randomized to placebo or 1 of 7 doses of active treatment. A priori, the 8 dosage assignments were combined into 4 treatment groups: placebo, low dose, medium dose, high dose (Figure 1). Randomization was performed to provide for equal numbers of patients in each of the 4 treatment groups. The first phase of the study was a single-blind stabilization/run-in period of 1 to 4 weeks' duration. To be eligible for the study, patients had to develop moderate angina within 3 to 7 minutes on a treadmill test on day 1. Patients also had to show ≥20% improvement in total exercise time 5 minutes after administration of an 0.4 mg sublingual nitroglycerin tablet. Patients satisfying these 2 criteria wore placebo patches for the rest of phase I. To qualify for randomization to double-blind therapy, patients were required to fulfill the following stabilization criteria on 3 consecutive treadmill tests: (1) development of moderate angina between 2.5 and 7.5 minutes; and (2) a difference in time to moderate angina between consecutive tests of ≤15%. The last qualifying treadmill test of phase I was designated as the baseline, pretreatment test.

The second phase of the study was a double-blind, parallel, forced titration period of 6 weeks' duration. The parallel dosage assignments were 0, 15, 30, 45, 60, 75, 90 and 105 mg/24 hours of transdermally applied nitroglycerin. The titration sequence consisted of weekly dose increments with all patients randomized to active drug receiving patches delivering 15 mg/24 hours of nitroglycerin for the first week. After each subsequent week of phase II the dosage was increased by 15 mg/24 hours until the randomized dosage assignment was achieved for each patient, after which the dosage remained constant for the remainder of the double-blind period. As the titration phase proceeded, the number of patches increased weekly, with the number of active and placebo patches varying to provide for proper dose assignment and blinding. All patches were worn on the upper body for a continuous 24-hour period and were replaced with fresh patches daily. During the titration sequence, treadmill tests were performed at the beginning of each titration week with a triad of tests performed at 0, 4 and 24 hours after patch application. The 0-hour test was performed with the previous day's patch in place, and the 4- and 24-hour tests were performed with new patches from the next week's sequence in place. The third phase was a 2-week, double-blind, fixed dose period with the assigned titrated dose. At the end of phase III, another series of 0-, 4- and 24-hour treadmill tests were performed. Approximately 1 to 2 hours after the 24-hour test, patients were again given a 0.4 mg sublingual tablet of nitroglycerin, and 5 minutes later performed a final treadmill test.

The last phase of the study was an optional 2-week, double-blind detitration period during which the transdermal nitroglycerin dose was gradually reduced to zero.

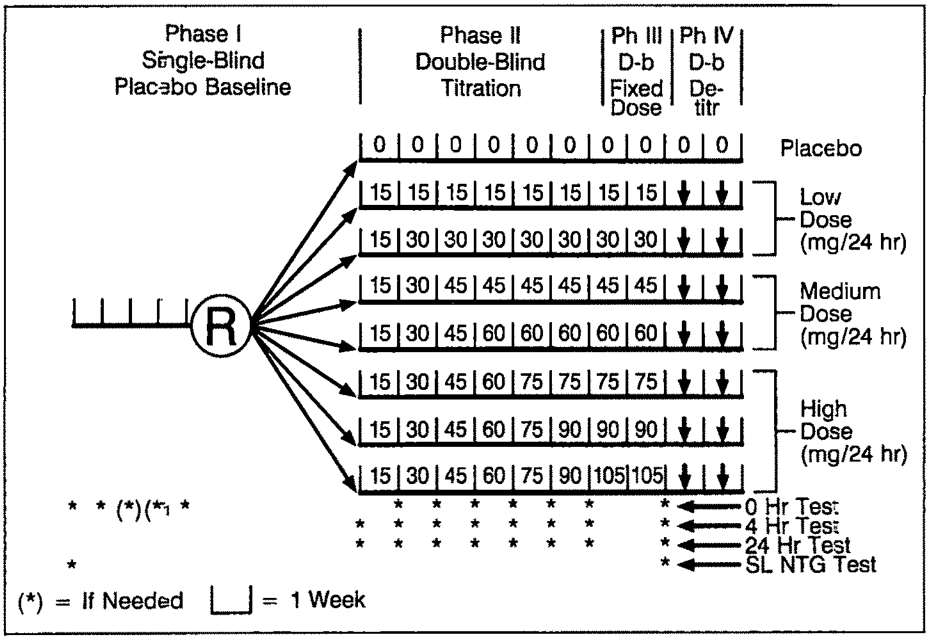

**FIGURE 1. Study design. D-b = double-blind; Ph = phase; R = randomization; SL NTG = sublingual nitroglycerin challenge; ↓ = detitration.**

The protocol was reviewed and approved by the appropriate human investigational review committees at each study center before initiation and all patients gave written informed consent before enrolling in the trial.

**Patient selection:** Patients were recruited from 68 centers across the United States. The participating centers are listed in the Appendix. Patients were considered for enrollment if they were outpatients, ≥21 years of age, of any race and either sex, with a primary diagnosis of stable effort-induced angina pectoris. Patients were also required to have objective evidence of myocardial ischemia. For patients with analyzable ST segments, the objective criterion for myocardial ischemia consisted of an ST segment depression of ≥1 mm during the initial treadmill test; for patients whose ST segments were not analyzable, objective evidence of disease was either angiographic evidence of significant (>60%) narrowing of a major coronary artery, a documented myocardial infarction or a positive thallium stress test.

Patients were excluded from entry if they had concomitant conditions that might interfere with the assessment of their angina (e.g., hiatus hernia, peptic ulcer disease, aortic stenosis, intermittent claudication). Patients were also excluded if they had had a myocardial infarction or coronary revascularization procedure within 3 months of enrollment. Other reasons for exclusion were: presence of a pacemaker; uncontrolled hypertension; brittle or uncontrolled diabetes; and significant hepatic, renal or hematologic disease. Patients were not allowed to take any long-acting antianginal medications during the trial except $\beta$ blockers (provided the dosage was unchanged during the trial). Other excluded medications were vasodilators (e.g., hydralazine, dipyridamole, prazosin) and aspirin in dosages exceeding 325 mg/day.

**Treadmill stress test:** A standard Bruce protocol treadmill test (starting at stage 1) was used for all stress tests. All exercise tests (0, 4, 24 hours) were scheduled at the same time each day for any given patient. Tests were performed ≥2 hours after a light meal. Electrocardiographic monitoring during the treadmill tests used the lead showing the maximal ST depression during the initial phase I test. Blood pressure, heart rate and ST-segment deviation were recorded just before exercise, at the end of each 3-minute stage completed, at the development of moderate angina and at the end of the test.

**Anginal frequency/symptomatology:** Attacks of angina pectoris and use of sublingual nitroglycerin for its relief were recorded daily in diaries; the patient's diary was reviewed each week with the patient for completeness and accuracy. Three symptoms (headache, dizziness and nausea) were solicited prospectively in the weekly diaries. Other adverse experiences were collected by open-ended questioning of patients during the clinic visits.

**TABLE I** Baseline Group Characteristics

| | Placebo | Low Dose | Medium Dose | High Dose |
|---|---|---|---|---|
| No. of pts. | 136 | 138 | 138 | 150 |
| Age (yr) | 63 | 64 | 62 | 63 |
| Gender (%) | | | | |
| Men | 83 | 83 | 82 | 80 |
| Women | 17 | 17 | 18 | 20 |
| Race (%) | | | | |
| White | 81 | 90 | 87 | 91 |
| Black | 13 | 6 | 11 | 6 |
| Other | 7 | 4 | 2 | 3 |
| $\beta$ blockers (%) | | | | |
| Never | 29 | 17 | 23 | 28 |
| Withdrawn | 23 | 20 | 21 | 21 |
| Continued | 49 | 62 | 56 | 51 |
| Angina/wk (median) | 2.7 | 3.5 | 3.5 | 3.0 |
| SL NTG/wk (median) | 1.0 | 1.7 | 1.4 | 1.0 |
| Supine BP (mean) | | | | |
| Systolic | 128 | 132 | 130 | 136* |
| Diastolic | 78 | 80 | 79 | 79 |
| Supine HR (mean) | 66 | 66 | 65 | 65 |

*$p < 0.05$ versus placebo.
BP = blood pressure; HR = heart rate; SL NTG = sublingual nitroglycerin.

**Trial organization:** A Steering Committee (Appendix) maintained responsibility for organization and execution of the study. An independent Safety Committee (Appendix) was charged with monitoring for the occurrence of serious adverse events.

**Statistical analysis:** Data from all centers were pooled for purposes of statistical analyses. All analyses were performed on an intent to treat basis. For efficacy analyses, a priori, the 8 dosage assignments were combined into 4 treatment groups: placebo, low dose (15 and 30 mg/24 hours), medium dose (45 and 60 mg/24 hours), and high dose (75, 90 and 105 mg/24 hours). The a priori primary efficacy variable was symptom-limited treadmill walking time (i.e., time to moderate angina, or, in its absence, total walking time to end points such as fatigue, shortness of breath, or for end points related to safety concerns). Secondary end points of treadmill testing were time to 1 mm ST depression and percentage of patients achieving a ≥20% increase in walking time (treatment success). The primary efficacy analysis was the comparison of the changes from baseline between treatment groups after the first 2 weeks of a fixed dose (with each treatment group compared to concurrent placebo). With use of 2-sample *t* tests incorporating unequal variances, groups receiving active treatment were tested separately against placebo. All treatment groups were also compared with those taking placebo after the first 4- and 24-hour double-blind treadmill tests and at the end of phase III with use of 1-way analysis of covariance with baseline as a covariate and multiple comparisons techniques. Changes from baseline in diary data of anginal fre-

**TABLE II** Changes in Total Treadmill Time and Time to 1 mm ST Depression Four and 24 Hours After Initial Application of Double-Blind Patches

| | Mean (±SEM) Changes from Baseline (seconds) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 4 Hours After Application | | | | 24 Hours After Application | | | |
| Treatment Group | No. | Total Time | No. | Time to 1 mm ST | No. | Total Time | No. | Time to 1 mm ST |
| Placebo | 132 | 15 ± 4 | 109 | 8 ± 7 | 131 | 26 ± 4 | 108 | 21 ± 7 |
| Low dose | 138 | 48* ± 5 | 118 | 56* ± 7 | 134 | 35 ± 4 | 116 | 28 ± 7 |
| Medium dose | 134 | 51* ± 5 | 113 | 53* ± 7 | 135 | 31 ± 5 | 113 | 17 ± 7 |
| High dose | 147 | 48* ± 5 | 117 | 56* ± 7 | 146 | 24 ± 4 | 117 | 14 ± 6 |

*Statistically significantly different from placebo at the 0.05 level.

A smaller number of patients were evaluable for ST depression because approximately 17% of electrocardiograms at baseline were uninterpretable for that variable.

SEM = standard error of the mean.

quency and sublingual nitroglycerin use were analyzed using nonparametric methods (Mann-Whitney rank sum test for between-treatment comparisons and Wilcoxon signed rank test for within-treatment comparisons).

## RESULTS

A total of 751 patients were enrolled into the study. Five hundred sixty-two were randomized to double-blind therapy, with 136 allocated to placebo, 138 to low-dose, 138 to medium-dose, and 150 to high-dose nitroglycerin. The 4 groups were well balanced with regard to baseline characteristics (Table I) and, except for a slightly higher supine systolic blood pressure in the high-dose group, there were no statistically significant differences between groups in any of the variables. In all, 455 patients (81%) completed the study (86% placebo, 78% low dose, 83% medium dose, 77% high dose).

**Exercise testing:** The baseline exercise tests for the treatment groups were comparable and were not statistically different. All patients terminated their baseline exercise test for moderate angina. Total treadmill times (mean ± standard deviation) were 322 ± 79 seconds for the placebo group, 306 ± 73 seconds for the low-dose group, 309 ± 77 seconds for the medium-dose group, and 321 ± 74 seconds for the high-dose group.

Four hours after application of the first set of double-blind patches (15 mg/24 hours for all patients receiving active treatment because of the step-up titration sequence of the study), the mean changes in total walking time from baseline were greater in the active treatment groups than in the placebo group. The difference of 34 seconds between the 3 pooled active treatment groups and placebo group was statistically significant (Table II, Figure 2).

Twenty-four hours after the initial patch application (15 mg/24 hours for all active treatment patients), mean changes in total walking times were generally similar for all treatment groups. No statistically significant difference between the pooled active treatments and placebo groups was observed (Table II, Figure 2). In subsequent titration weeks, the acute 4- and 24-hour response to dose increases showed no statistically significant differences between any active treatment and placebo.

The same pattern of acute and 24-hour response was observed for time to onset of 1 mm ST-segment depression (Table II).

After 2 weeks of double-blind, fixed-dose therapy, mean total walking time 24 hours after patch application increased compared with baseline in all of the treatment groups, but there were no statistically significant differences or trends in the magnitude of these increases between any active treatment group and concurrent placebo (Table III). Similar results were seen

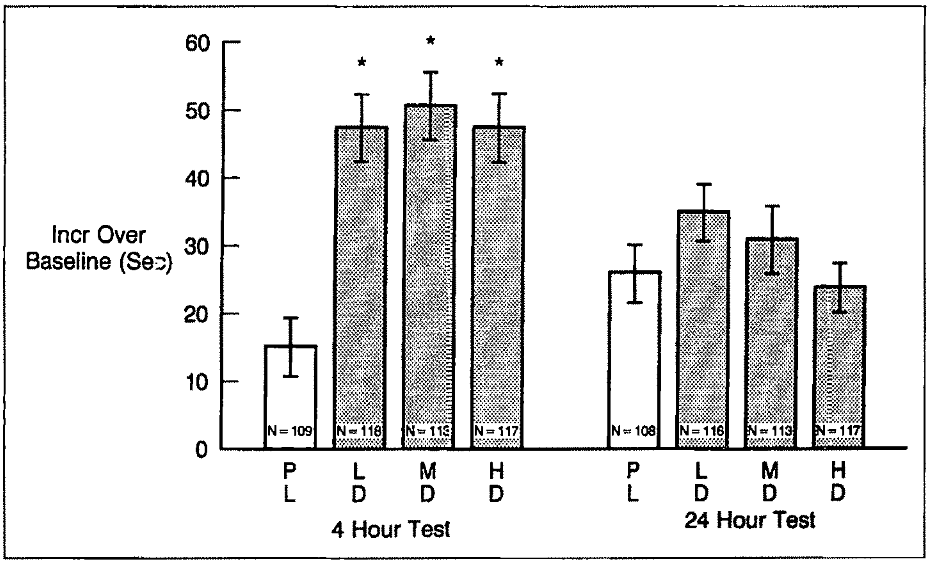

**FIGURE 2. Acute exercise tolerance data. Four hours after initial application of double-blind patches, the increase (incr) in treadmill exercise time over baseline was statistically significantly greater for the active treatment groups than for placebo. This difference was no longer evident 24 hours after patch application. HD = high-dose group; LD = low-dose group; MD = medium-dose group; PL = placebo group; *p <0.05 versus placebo.**

at 4 hours after patch application after 2 weeks of fixed-dose therapy (Table III). There were no significant differences between the groups in time to development of 1 mm ST-segment depression at 4 or 24 hours (Table III). The percentages of treatment "successes" in each treatment group were similar (range 37 to 50%). There were no statistically significant differences in the percentage of successes between any active treatment group and the corresponding placebo group. Because some patients terminated their treadmill tests for symptoms other than moderate angina after randomization, in addition to the aforementioned analysis, survival analysis techniques were used to incorporate the censoring of total treadmill time for those patients failing to develop moderate angina on the treadmill. The differences between the active treatment and placebo groups were, once again, not statistically significant either 4 or 24 hours after patch application, and confirmed the original analysis.

Similarly, after 8 weeks of double-blind treatment, placebo and active treatments were indistinguishable for total walking time and time to the onset of 1 mm ST depression (Table IV).

Individual dose groups were analyzed in a post hoc fashion. There was no apparent dose-related trend in any of the exercise end points. Only the difference for the 30 mg/24 hour treatment sequence versus placebo reached nominal (not corrected for multiple comparisons) statistical significance after 8 weeks of treatment (Figure 3). Subsequent to these results, the baseline characteristics of the 30 mg/24 hour group were analyzed for any uniqueness. There were no identifiable variables that set this group apart from the other groups.

**TABLE III** Changes from Baseline After Initial Two Weeks of an Assigned Dosage

| | Mean (±SEM) Changes from Baseline (seconds) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 4 Hours After Application | | | | 24 Hours After Application | | | |
| Treatment Group | No. | Total Ex. Time | No. | Time to 1 mm ST | No. | Total Ex. Time | No. | Time to 1 mm ST |
| Low dose | | | | | | | | |
| Placebo | 129 | 52 ± 7 | 106 | 29 ± 8 | 129 | 53 ± 6 | 106 | 35 ± 8 |
| Active | 118 | 54 ± 6 | 101 | 39 ± 9 | 118 | 54 ± 6 | 101 | 34 ± 7 |
| Medium dose | | | | | | | | |
| Placebo | 125 | 68 ± 8 | 103 | 40 ± 9 | 125 | 72 ± 8 | 103 | 47 ± 9 |
| Active | 122 | 71 ± 8 | 102 | 40 ± 10 | 122 | 69 ± 7 | 102 | 37 ± 9 |
| High dose | | | | | | | | |
| Placebo | 120 | 82 ± 9 | 98 | 46 ± 9 | 120 | 87 ± 9 | 98 | 54 ± 9 |
| Active | 115 | 72 ±8 | 93 | 56 ± 10 | 114 | 79 ± 8 | 93 | 64 ± 9 |

Ex. = exercise; SEM = standard error of the mean.

**TABLE IV** Changes from Baseline After Eight Weeks of Double-Blind Therapy

| | Mean (±SEM) Changes from Baseline (seconds) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 4 Hours After Application | | | | 24 Hours After Application | | | |
| Treatment Group | No. | Total Ex. Time | No. | Time to 1 mm ST | No. | Total Ex. Time | No. | Time to 1 mm ST |
| Placebo | 117 | 79 ± 9 | 97 | 44 ± 10 | 118 | 86 ± 9 | 97 | 53 ± 9 |
| Low dose | 108 | 89 ± 8 | 92 | 54 ± 10 | 109 | 88 ± 8 | 93 | 55 ± 10 |
| Medium dose | 115 | 93 ± 8 | 96 | 49 ± 10 | 116 | 90 ± 8 | 97 | 50 ± 10 |
| High dose | 115 | 76 ± 8 | 93 | 57 ± 10 | 115 | 82 ± 8 | 93 | 67 ± 9 |

Ex. = exercise; SEM = standard error of the mean

Data analyses were performed to identify a subgroup of patients whose exercise response to the initial application of transdermal nitroglycerin did not attenuate with continuous therapy. Subgroups of individual and combination groupings of race, sex, β-blocker use and baseline characteristics were evaluated. No subgroup of responders could be identified that sustained the improvement in exercise capacity noted after the initial 4 hours of patch application.

A steady increase in treadmill performance was seen in all treatment groups as patients progressed through the study's 28 exercise tolerance tests. Figure 4 shows the weekly initial 0-hour tests for the placebo group

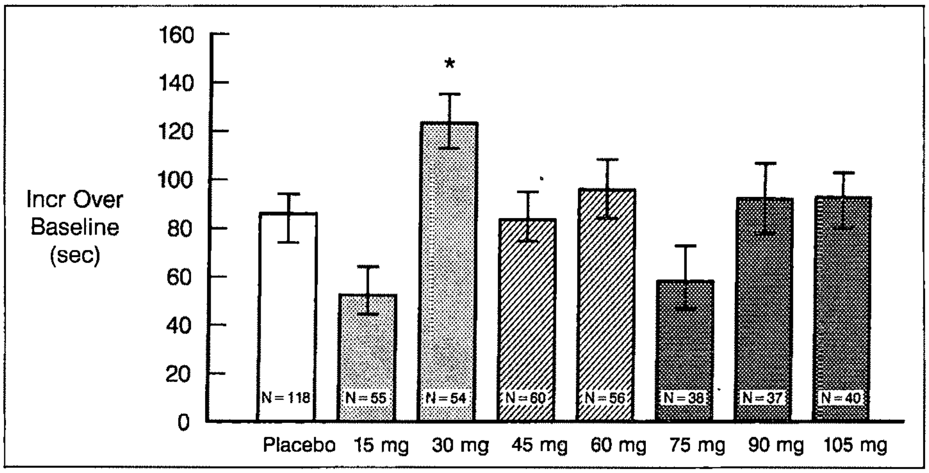

**FIGURE 3. Chronic exercise tolerance data after 8 weeks of double-blind therapy. All groups showed increase (Incr) in treadmill performance over baseline at the end of the trial. Only the 30 mg/24 hour group demonstrated a nominally statistically significant increase that was greater than the placebo response. *$p < 0.05$ over placebo.**

**TABLE V** Exercise Response to Sublingual Nitroglycerin

| Treatment Group | Mean Total Exercise Duration (seconds) | | | | | |
|---|---|---|---|---|---|---|
| | Initial Visit | | | Final Double-Blind Visit | | |
| | Baseline | SL NTG | Mean % Change | Baseline | SL NTG | Mean % Change |
| Placebo | 300 ± 6 | 412 ± 9 | 39 | 410 ± 13 | 473 ± 12 | 19 |
| Low | 286 ± 6 | 388 ± 7 | 37 | 394 ± 12 | 428 ± 11 | 11 |
| Medium | 290 ± 6 | 400 ± 8 | 39 | 396 ± 11 | 426 ± 12 | 9 |
| High | 298 ± 6 | 406 ± 7 | 38 | 403 ± 11 | 419 ± 11 | 5 |

SL NTG = sublingual nitroglycerin challenge.

from the start of the trial through the 8 weeks of double-blind therapy. By the end of the study, treadmill time had increased by approximately 25% and one fourth of these placebo-treated patients terminated the test for fatigue-related symptoms rather than for angina (even though angina was the required termination end point for all patients at the baseline treadmill test). This same pattern of improvement in total exercise time and change in exercise end point was seen in each of the active treatment groups.

**Exercise tests — sublingual nitroglycerin challenge:** The total treadmill walking times after the administration of a 0.4 mg sublingual nitroglycerin tablet at the first visit of phase I and after 8 weeks of double-blind therapy are listed in Table V. At the end of the study, mean total walking time after sublingual nitroglycerin increased in comparison to the initial sublingual nitroglycerin challenge in all 4 treatment groups. The greatest increase at the end of the study occurred in the placebo group. A partial attenuation of response to sublingual nitroglycerin in the active transdermal nitroglycerin treatment groups followed a dose-related pattern.

**Anginal attack frequency by diary:** The median frequency of anginal attacks at baseline for all randomized patients ranged from 2.7 to 3.5 attacks per week. During the double-blind period, anginal attack rate generally decreased more in the transdermal nitroglycerin treatment groups than in the placebo group but the differences were not statistically significant.

The median use of sublingual nitroglycerin at baseline ranged from 1.0 to 1.7 tablets per week. During the double-blind portion of the trial, the median change from baseline in use of sublingual nitroglycerin was 0.0 tablets per week for all treatments.

Because approximately 25% of all patients during the baseline period did not have symptomatic attacks or take sublingual nitroglycerin, a post hoc subgroup analysis of treatment effect on symptoms was conducted in patients in the top quartile of anginal frequency at baseline. Patients in this top quartile had over 7 attacks per week at baseline. In this post hoc subgroup, greater reductions in anginal frequency were observed for all patients taking active nitroglycerin treatment than for those taking placebo at both 2 and 8 weeks, although differences in the medium-dose group were small at 2 weeks (Figure 5). Each group who received active ni-

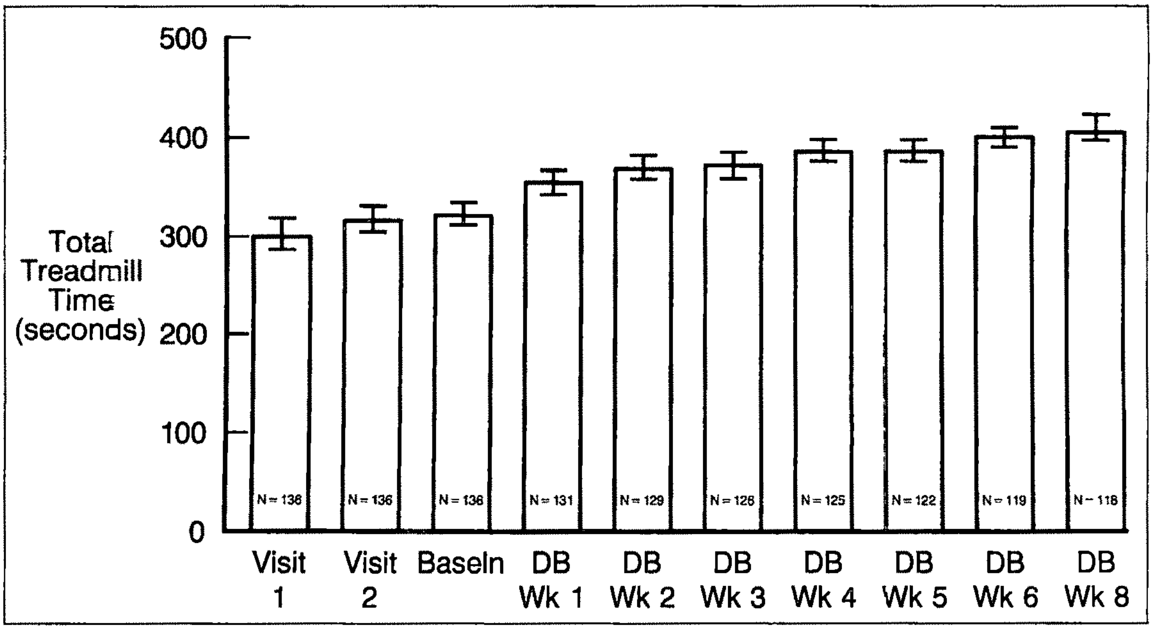

**FIGURE 4. Exercise tolerance data during placebo therapy. Total treadmill exercise time increased over course of the trial in patients with angina randomized to placebo. Although all patients were required to have angina-limited exercise performance at the baseline visit, one quarter of the patients terminated at double-blind week 8 for fatigue-related reasons even though they were exercising for longer periods. Baseln = baseline treadmill test immediately before randomization; DB = double-blind; Wk = week.**

troglycerin treatment by itself, was not statistically significantly different from the placebo group (possibly because the sample sizes were 18 to 29 patients per group). When patients who received active treatment were combined (as seemed reasonable since the response rates were similar for each active treatment group) and then compared with the placebo group, the threefold greater reduction in anginal frequency at the end of 8 weeks of double-blind therapy was different from those taking placebo ($p < 0.05$ by 2-sided Mann-Whitney Test). This result should be interpreted with caution as it resulted from a post-hoc analysis.

Exercise performance was evaluated subsequently for this subgroup of patients in the top quartile of baseline frequency of angina. There were no differences in exercise performance compared with that in the placebo group, and no correlation of treadmill response to decrease in anginal attack rate was found.

**Hemodynamic effects:** Four hours after the initial application of active (15 mg/24 hours) patches, supine and standing blood pressures were reduced compared with blood pressures in the parallel placebo group (e.g., a representative group response is shown in Figure 6). After the first week of double-blind therapy, and for the rest of the study, differences in blood pressure between active and placebo groups were no longer evident. The orthostatic blood pressure response to 30 seconds or 2 minutes of standing was similar in all treatment groups at baseline and during the study.

**Safety evaluations:** Four deaths occurred during the study, 2 during the baseline phase and 2 during the double-blind phase. The 2 post randomization deaths occurred in patients randomized to placebo. In each case, death followed an acute myocardial infarction. Patients who received 24-hour therapy were withdrawn for other serious cardiovascular events: 11 with myocardial infarction, 8 with unstable angina and 5 with arrhythmias. These episodes were distributed evenly among all of the treatment assignments and did not appear to be drug or dose-related. No serious adverse experiences occurred during the withdrawal phase of the study.

Headache was the most frequent cause of discontinuation during the double-blind phase of the trial. All

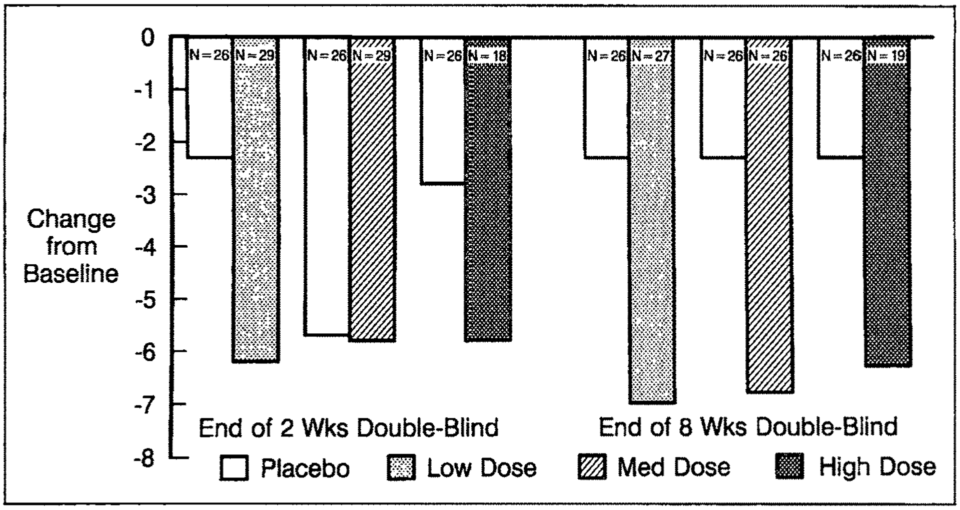

**FIGURE 5. Median changes in anginal attack frequency during the double-blind period for the subset of patients in the top quartile of baseline angina. These 103 patients had >7 attacks of angina per week at baseline. In a post-hoc analysis, the difference between placebo and active therapy at week 8 was statistically significant at the p = 0.05 level.**

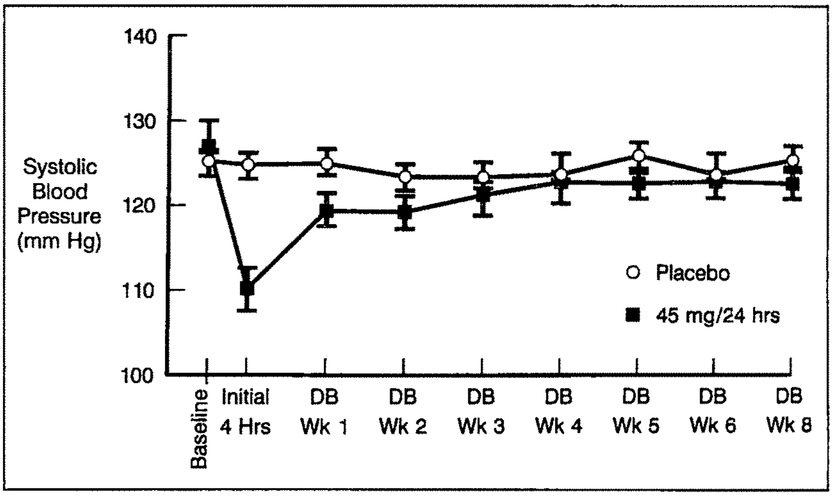

**FIGURE 6. Standing systolic blood pressures in the placebo and 45 mg/24 hour groups during the trial. The 45 mg/24 hour group is representative of the response pattern seen in all the other active groups. There was an initial hypotensive response to the first 4 hours of patch application of approximately 15 mm Hg that was no longer evident after the first day of the trial. A similar pattern was observed for supine blood pressure. DB = double-blind.**

**TABLE VI** Frequent Adverse Events (% patients with event)

| Event | Placebo | Low Dose | Medium Dose | High Dose |
|---|---|---|---|---|
| Headache | 56 | 78 | 82 | 81 |
| Nausea | 14 | 26 | 21 | 15 |
| Dizziness | 23 | 30 | 28 | 26 |
| Application site reaction | 18 | 26 | 27 | 30 |
| Fatigue | 12 | 11 | 12 | 10 |
| URI | 10 | 7 | 8 | 10 |
| Pain | | | | |
| General | 7 | 5 | 5 | 6 |
| Back | 5 | 5 | 3 | 3 |
| Skel-musc | 4 | 7 | 5 | 5 |
| Dyspnea | 5 | 4 | 6 | 8 |
| Diarrhea | 4 | 6 | 4 | 5 |

Skel-musc = skeletal muscle; URI = upper respiratory infection.

discontinuations due to headache were among patients receiving active therapy (12 in the low-dose, 5 in the medium-dose and 12 in the high-dose group). Headache was most frequently reported at the beginning of the double-blind phase of the trial (Figure 7) when all active treatment patients were receiving 15 mg/24 hours. The frequency of headache abated in all active treatment groups over the first 3 weeks of the double-blind period despite the fact that dosage was increasing in the medium- and high-dose patients. Other adverse experiences encountered during the trial were of a nature and frequency anticipated from transdermal nitroglycerin patches. A listing of the most frequent adverse events appears in Table VI. There were no remarkable changes in any of the physical examinations or laboratory tests performed during the trial. Methemoglobin levels, of particular interest because of the use of chronic, high dosages of nitroglycerin, were essentially unchanged from baseline values during the study.

## DISCUSSION

This large, well-controlled trial has demonstrated that tolerance to exercise treadmill performance develops within 24 hours after the first application of a transdermal nitroglycerin system and that, on average, continuous transdermal application is not an effective treatment for exercise-induced angina. The patient population in the trial was clearly responsive to the acute effects of transdermally applied nitroglycerin because exercise variables were statistically improved 4 hours after the initial patch application.

These results are consistent with most small, well-controlled trials that have previously explored transdermal nitroglycerin tolerance,[13-19] and with the conclusion of a meta-analysis study performed on most of the randomized trials in the literature.[20] Similar results have been reported for other nitrate preparations when used chronically.[21-23] The consistent finding among these studies is the loss of exercise efficacy to organic nitrates during therapeutic regimens that maintain constant, elevated nitrate blood concentrations.

The study also demonstrated that larger doses of transdermally applied nitroglycerin, up to 105 mg/24 hours, did not overcome this tolerance. There was also no apparent dose-response relation noted during chronic therapy. Thus, failure to sustain efficacy of transdermal systems cannot be ascribed to differences in dosage used or to inadequate dose levels.

Several recent well-controlled trials have suggested that the inclusion of a nitrate-free interval into the transdermal patch application schedule will avoid this development of tolerance.[24-27] The need for a nitrate-free interval to preserve continued efficacy is apparently not unique to patches; several recent studies have indicated that oral nitrate preparations also require a daily nitrate-free period to maintain efficacy.[28,29]

The results of this trial also have shown that, paralleling the loss of treadmill performance, there was a rapid attenuation of the hypotensive effect of transdermal nitroglycerin. A rapid loss of the systemic hemodynamic effects of nitrates has been reported by oth-

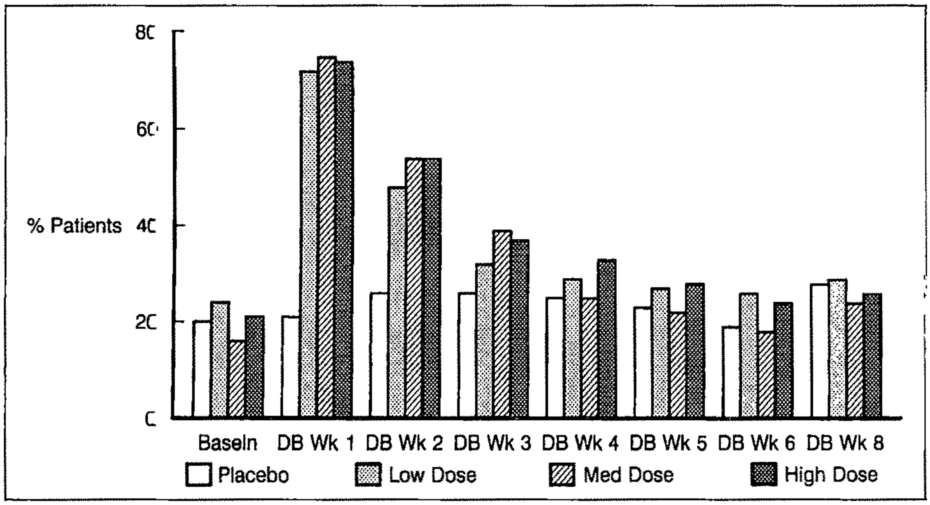

**FIGURE 7. Incidence of headache during the trial. Headache was a frequent adverse effect in patients receiving active patch on initiation of the double-blind (DB) study. This incidence gradually returned to a rate similar to effects with placebo after 4 weeks of chronic therapy. Headache in the high-dose group was no different than that in the placebo group at the end of the trial even though the highest dosages were administered during weeks 5 to 8. Other abbreviations as in Figure 4.**

ers,[30,31] and is consistent with the hypothesis that the mechanism of action for nitrate's improving exercise capacity is through reduced preload and afterload.

Partial tolerance may have developed to the treadmill effects of sublingual nitroglycerin after chronic transdermal nitroglycerin therapy. Although all the active treatment groups showed an improvement over baseline in exercise capacity to a sublingual nitroglycerin challenge, this improvement was clearly not as great as that of the placebo group. Moreover, the higher dose groups showed the greater attenuation of effect. Other studies using treadmill testing end points have not shown cross-tolerance between either transdermal nitroglycerin, transdermal isosorbide dinitrate or oral nitrates and the sublingual preparations.[13,22] The apparent discrepancy between the present trial and these others is unexplained, but may be due to the fact that previous studies did not administer long-acting nitrates at doses well above the recommended clinical range as was done in the present study (e.g., 105 mg/24 hours is 7 times the maximal recommended dose). Interestingly, the amount of sublingual nitroglycerin used for symptomatic angina decreased more in the active treatment groups than in the placebo group, suggesting a possible dissociation between the effects of the drug on treadmill performance and on symptoms induced by daily activity.

This study found no overall effect of transdermal nitroglycerin on daily anginal frequency. However, approximately 25% of patients in each treatment group did not have symptomatic angina at baseline (symptomatic angina was not an entrance criterion for this trial). Because patients without symptoms may have had a diluting effect on any treatment comparisons, patients in the top quartile of anginal frequency were examined for changes in anginal attack rate. This analysis revealed that active treatment reduced attack rates 3 times greater than matching placebo. This effect on anginal attack rate persisted throughout the trial and was more evident at the end of the study than at the beginning. However, this observation must be interpreted with caution since the analysis of the top quartile of patients was not planned in advance. The finding was not matched by improved exercise tolerance in this group.

The lack of a relation between the effects of transdermal nitroglycerin on exercise tolerance and on daily anginal frequency has been reported in another double-blind, placebo-controlled trial.[3] Additionally, the possibility of a dichotomy of treadmill and symptomatic efficacy of nitrates is not inconsistent with the large body published reports on nitrates. Whereas, well-controlled clinical trials that have used exercise end points usually demonstrate rapid tolerance,[13-19] other well-controlled trials that have used symptomatic end points usually have documented sustained reductions in anginal frequency during continuous patch administration.[3,5,8-12] Most of these nitrate trials documenting symptomatic improvement have studied patient populations with ≥7 attacks of angina per week at baseline or during placebo treatment, consistent with the subgroup analysis of this trial.

Increase in exercise tolerance time is the appropriate and accepted end point for evaluation of antianginal drugs because angina pectoris is usually precipitated by an exercise-induced increase in myocardial oxygen demand. However, the suggestion in this trial of a difference between exercise tolerance test results and a decrease in anginal symptomatology, at least in some patients, is intriguing. Possible explanations for the dichotomy of responses include chronic nitrate effects on coronary vasomotor tone[32,33] or effects mediated by inhibition of platelet aggregation.[34] These effects could result in a decrease in symptoms in patients whose angina is wholly or partly a result of decreased coronary blood supply rather than increased demand. Such an explanation for the observed phenomenon is speculative and must be regarded strictly as a hypothesis at this time. Further exploration would appear to be warranted by a prospective clinical trial measuring both exercise tolerance and symptomatic end points in patients with a significant degree of spontaneous angina pectoris during their routine daily activities.

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## APPENDIX

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# Digoxin-Induced Vasoconstriction of Normal and Atherosclerotic Epicardial Coronary Arteries

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**This study evaluated the effect of bolus infusion of digoxin (0.014 mg/kg in 10 minutes, intravenously) on large coronary arteries measured by quantitative digital angiography. Twenty-two patients (mean age ± standard deviation 47 ± 12 years) divided into 3 groups were studied. The effects of digoxin infusion (after 10 and 20 minutes) and sublingual administration of isosorbide dinitrate were investigated in group I (patients with angiographically normal coronary arteries, n = 9) and in group II (patients with atherosclerotic coronary arteries, n = 8). To determine whether the effects of digoxin were mediated by activation of $\alpha$-adrenergic receptors, coronary angiography was performed in group III after $\alpha$-adrenoceptor blockade (phentolamine 0.11 mg/kg, intravenously) (n = 5). Ten minutes after the end of digoxin infusion, the cross-sectional area decreased from 7.7 ± 4.1 to 6.0 ± 2.2 $mm^2$, and after 20 minutes to 5.6 ± 2.6 $mm^2$ ($p < 0.05$) in group I. Isosorbide dinitrate reverted digoxin-induced vasoconstriction as cross-sectional area increased to 8.5 ± 3.4 $mm^2$ (p = not significant versus baseline). Twenty minutes after digoxin infusion, heart rate significantly decreased from 79 ± 16 to 74 ± 13 beats/min ($p < 0.01$). Ten minutes after digoxin infusion, peripheral vascular resistance increased significantly from 1,396 ± 693 to 1,693 ± 984 dynes $\cdot$ s $\cdot$ $cm^{-5}$ ($p < 0.05$), whereas cardiac output did not change. Twenty minutes after digoxin infusion, minimal stenosis diameter decreased significantly from 1.6 ± 0.5 to 1.4 ± 0.5 mm ($p < 0.05$) in group II. Again, isosorbide dinitrate reverted digoxin-induced vasoconstriction as minimal stenosis diameter increased (p = not significant versus control values). In group III, $\alpha$-adrenoceptor blockade with phentolamine did not prevent the decrease in coroary artery diameter in patients with angiographically normal coronary arteries, from 2.3 ± 0.7 to 1.9 ± 0.7 mm ($p < 0.001$).**

**Thus, bolus infusion of digoxin induced vasoconstriction of normal epicardial coronary arteries and reduced minimal stenosis diameter in patients with coronary artery disease. Digoxin-induced vasoconstriction was not mediated by an $\alpha$-adrenergic mechanism and was revertedby sublingual administration of isosorbide dinitrate.**

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For >200 years, digitalis glycosides have occupied a prominent place in the management of congestive heart failure and certain arrhythmias. However, intravenous administration of cardiac glycosides increases peripheral vascular resistances[1] and constricts small coronary resistance vessels.[2] The elevation of arterial pressure induced by cardiac glycosides was not abolished by ganglionic blockade, demonstrating a direct action on the vascular smooth muscle,[1] although an $\alpha$–adrenergic-mediated vasoconstriction has also been hypothesized[3] Peripheral vasoconstrictor effects of digitalis have been documented clinically,[4] including cardiogenic shock[5] or hypertension.[6] These observations indicate the need for caution when digitalis glycosides are administered acutely, particularly in situations in which transient increases in peripheral resistance would be deleterious.

There are no data to date on the effects of cardiac glycosides on normal or diseased human epicardial coronary arteries. Under normal conditions, digitalis-induced vasomotion of epicardial coronary arteries is probably of minor physiologic importance. However, changes in coronary diameter may have a paramount importance in presence of atherosclerotic lesions. In fact, it has been demonstrated that coronary stenoses are not rigidly fixed,[7] and an important property of the stenosis contributing to variation in its pressure loss is the minimum lumen diameter.[8] Whether the digoxin produces vasomotion of large human coronary arteries is unclear. Accordingly, the present study was designed

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to examine the effects of digitalis on normal and atherosclerotic epicardial coronary arteries in humans. The role of $\alpha$-adrenergic receptrs in the response of intravenous administration of digitalis was also assessed.

## METHODS

**Study group:** Twenty-two subjects (13 men and 9 women) ranging in age from 37 to 71 years (mean 47 ± 12) were included in the study. All patients were referred to our institution for evaluation of chest pain syndrome and they had clinical indication for coronary angiography.[9] All patients gave written informed consent before the study and the protocol was approved by the human research committee of our institution. No patient had angina at rest, previous or acute myocardial infarction, diabetes mellitus, arterial hypertension or valvular heart disease. Patients were classified into 3 groups: group I ($n = 9$), subjects with angiographically normal coronary arteries; group II ($n = 8$), patients with coronary artery disease on the basis of diagnostic angiograms; group III ($n = 5$), patients without coronary artery disease pretreated with phentolamine. All subjects underwent right and left-sided cardiac catheterization in the morning, in the supine position, after an overnight fast. No drugs were allowed in the week preceding the study.

Diagnostic coronary angiography was performed by a standard percutaneous femoral approach using the Judkins technique. A 7Fr Swan-Ganz heparinized catheter was placed through the right femoral vein into the pulmonary artery. In subjects with normal coronary arteries, pulmonary artery, right atrial and capillary wedge pressures were periodically measured; cardiac output was measured by thermodilution.

**Study protocol:** Digoxin was infused at a dose of 0.014 mg/kg intravenously over a 10-minute period[10] using a Harvard pump. In groups I and II, coronary angiography was performed under baseline conditions, 10 and 20 minutes after the end of digoxin infusion, and 5 minutes after sublingual administration of 5 mg of isosorbide dinitrate. A nonionic contrast medium (Iohexol, Omnipaque, Winthrop-Breon, Inc., New York), which had no significant hemodynamic effects,[11] was used. In group III, to determine whether the effect of digoxin was mediated by activation of $\alpha$-adrenergic receptors, in 5 subjects without coronary artery disease, coronary angiography was performed after $\alpha$-adrenergic blockade with phentolamine (0.11 mg/kg intravenously, bolus) in the control state and 20 minutes after digoxin infused at the same dose as previously described.

**Quantitative coronary angiography:** Coronary angiography was performed using a Siemens radiographic system. Cineangiograms were recorded at a rate of 50 frames/s. For quantitative analysis, end-diastolic cine frames were blindly videodigitized in the image analysis system (MIP-D, Mipron, Kontron electronics) in a 512 × 512 matrix with 8-bit gray scale after a 2× zooming. Automatic vessel segment contour detection was performed by a geometric edge-differentiation technique using a method previously described.[12] In brief, after interactive determination of a centerline within the vessel segment to be measured, the computer automatically generates a number of scanlines perpendicular to the centerline. The first and second derivative functions of densograms along each scanline are then computed, and the contour point is defined as 70% of the distance between the extrema of the first and second derivatives. With the use of the detected contour points, the computer then automatically generates a refined centerline of the vessel segment, and the edge-detection algorithm is repeated. Each individual scanline is smoothed by a second-order polynomial fit, and smoothing of the contour is obtained by averaging 3 neighboring scanlines. Calculation of the exact radiologic magnification factor of the measured segment is used to scale the data from pixels to millimeters.[13] The accurac and reproducibility of quantitative angiographic measurements was previously documented in our laboratory.[12] Cross-sectional area (CSA) was measured using the following formula: $CSA = D \cdot D \cdot 3.14/4$; where $D$ = coronary artery diameter.

In patients with coronary artery stenosis, we selected the view in which the stenosis appeared more severe in order to measure minimal coronary stenosis blood flow diameter, that is, correlated to coronary reserve.[8]

**Plasma level measurements of digoxin:** Venous blood samples for digoxin were obtained before and after digoxin infusion in 7 subjects with angiographically normal coronary arteries through the femoral vein, immediately placed on ice, promptly centrifuged at 4°C, and aliquots of plasma were stored at −20°C. Plasma levels of digoxin were determined by the immunofluorimetric assay.[14]

**Data and statistical analysis:** Aortic, wedge, pulmonary and atrial pressures were recorded by a computer-aided system for cardiac catheterization (Siecor, Siemens). Pressure waveform analysis was performed within a user-definable analysis window over 8 consecutive beats.[15] Results are expressed as mean ± standard deviation. Statistical analysis was performed by analysis of variance for repeated measures[16] using SYSTAT program,[17] and when a significant overall effect was detected, Tukey's test was applied to compare single values.[16] A Student $t$ test for paired data was used to compare the effect of digoxin on coronary diameter after phentolamine infusion in group III, and to compare the changes in digoxin plasma levels. Significant differ-

**TABLE I** Effects of Intravenous Digoxin on Hemodynamics in Subjects with Normal Coronary Arteries

| | Control | Digoxin Infusion (min) 10 | 20 | ISDN |
|---|---|---|---|---|
| Systolic arterial pressure (mm Hg) | 142 ± 21 | 152 ± 22 | 155 ± 21* | 143 ± 25 |
| Diastolic arterial pressure (mm Hg) | 74 ± 14 | 80 ± 12* | 78 ± 9 | 80 ± 10 |
| Wedge pressure (mm Hg) | 9 ± 3 | 9 ± 5 | 8 ± 4 | 7 ± 5 |
| Heart rate (beats/min) | 79 ± 16 | 75 ± 16 | 74 ± 213* | 84 ± 17 |
| Systemic vascular resistances (dynes · s · cm$^{-5}$) | 1,294 ± 639 | 1,535 ± 970* | 1,487 ± 786 | 1,510 ± 940 |
| Cardiac output (liters/min) | 5.5 ± 1.6 | 5.1 ± 1.5 | 5.2 ± 2.0 | 4.6 ± 2.5 |
| Right atrial pressure (mm Hg) | 6 ± 3 | 7 ± 3 | 7 ± 4 | 6 ± 3 |

*$p < 0.05$ compared with control.
ISDN = dinitrate isosorbide.

ences were assumed to be present when the p value was $<0.05$.

## RESULTS

All subjects had no evidence of regional wall motion abnormalities on left ventriculography.

**Group I: Responses to digitalis infusion in subjects with angiographically normal coronary arteries:** The infusion of digoxin increased the plasma level from 0.2 ± 0.3 to 11.2 ± 4.7 ng/ml ($p < 0.001$) in subjects without coronary artery disease. Coronary diameter in the control state was 3.0 ± 0.8 mm, and decreased significantly 10 minutes after digoxin administration to 2.8 ± 0.7 mm, reaching its maximum 20 minutes after the glycoside infusion (to 2.6 ± 0.7 mm, $p < 0.05$). Isosorbide dinitrate administrated sublingually reverted digoxin-induced vasoconstriction as coronary artery diameter increased to 3.2 ± 0.7 mm (p = not significant versus baseline). Similarly, cross-sectional area was reduced by 14% (from 7.7 ± 4.1 to 6.0 ± 2.2 mm$^2$) and 23% (5.6 ± 2.6 mm$^2$; $p < 0.05$) 10 and 20 minutes after digoxin infusion, respectively. The percent changes versus baseline of the cross-sectional area are shown in Figure 1. The hemodynamic changes after digoxin infusion and isosorbide dinitrate administration are summarized in Table I. Twenty minutes after digoxin infusion, heart rate significantly decreased by 12% (from 83 ± 23 to 73 ± 21 beats/min; $p < 0.05$). Peripheral vascular resistances increased significantly by a mean of 22% 10 minutes after digoxin administration (1,326 ± 693 to 1,693 ± 984 dynes · s · cm$^{-5}$; $p < 0.05$), whereas cardiac output did not change. Systolic aortic pressure at 20 minutes after digitalis infusion was significantly different from control value.

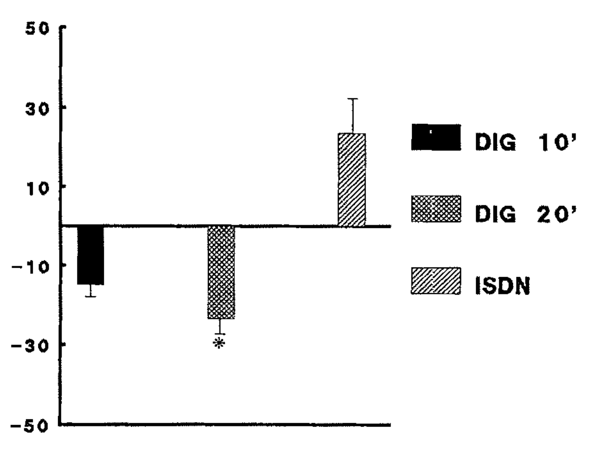

**FIGURE 1. Percent changes versus baseline of cross-sectional area after digoxin (DIG) infusion (10 and 20 minutes) and after sublingual administration of isosorbide dinitrate (ISDN) in patients with coronary artery disease. *$p < 0.05$ versus control.**

**Group II: Effects of digitalis in patients with atherosclerotic coronary arteries:** In patients with coronary artery disease, minimal stenosis diameter decreased from 1.6 ± 0.5 to 1.56 ± 0.4 mm, and to 1.42 ± 0.5 mm ($p < 0.05$) 10 and 20 minutes after digoxin infusion, respectively. Again, isosorbide dinitrate reverted digoxin-induced vasoconstriction, as minimal stenosis diameter increased to 1.6 ± 0.5 mm (p = not significant versus baseline). Systolic pressure increased significantly 10 and 20 minutes after digoxin administration, from 126 ± 30 to 133 ± 33mm Hg ($p < 0.05$) and to 132 ± 30 mm Hg ($p < 0.05$), respectively, whereas diastolic aortic pressure did not change significantly (from 73 ± 13 to 81 ± 16 mm Hg and to 78 ± 18 mm Hg 10 and 20 minutes after digoxin, respectively). Heart rate decreased 20 minutes after digoxin administration (fom 80 ± 16 to 73 ± 10 beats/min; $p < 0.05$).

**Effects of digoxin on coronary diameter in patients pretreated with phentolamine:** Coronary artery diameter also decreased significantly in the 5 patients pretreated with intravenous phentolamine, from 2.3 ± 0.7 to 1.9 ± 0.7 mm ($p < 0.001$). Similarly, cross-sectional area decreased from 4.7 ± 2.5 to 3.4 ± 2.1 mm$^2$ ($p < 0.01$) (Figure 2).

## DISCUSSION

The major finding of the present study is that intravenous administration of digoxin causes a significant reduction in normal and atherosclerotic epicardial coronary diameter in humans. This constriction is not mediated through an $\alpha$-adrenergic mechanism and is reverted by sublingual administration of nitrates. The increase in aortic pressure observed in the present study after digoxin infusion may have caused an increase in myocardial metabolic demand, which in turn should increase coronary arterial diameter and thus prevent a greater constriction.[18] However, an explanation for the decrease in coronary arterial diameter in response to digoxin is myogenic contraction in response to the increase in aortic pressure. Although such a mechanism has been shown by some investigators to contribute to the autoregulation of blood flow in certain vascular beds,[19] the potential contribution of a myogenic mechanism to coronary autoregulation has not been directly tested.[20]

Another possible explanation for the decrease in coronary diameter is the reduction in heart rate observed in the present study. In fact, a relation between heart rate and cross-sectional area of the artery has been demonstrated in dogs.[21] However, the change in heart rate is unlkely to be the entire explanation for the decrease in coronary diameter, since coronary vasoconstriction after ouabain administration was also observed in dogs in which heart rate did not change.[22] In addition, an in vitro study demonstrated that ouabain blocks the effect of basally released endothelium-derived relaxing factors from perfused coronary arteries in dogs and diminishes the effect of acetylcholine-released mediators on coronary arterial smooth muscle[23]; it has been demonstrated that the vascular effect of ouabain is mediated through an inhibition of sodium-potassium pump activity with increasing in calcium ion influx.[24] The presence of the muscoelastic arc in the compliant coronary stenosis provides a mechanism whereby digoxin may affect lumen caliber and thus flow resistance in patients with coronary artery disease.

**Differences from previous studies:** Previous reports on the effects of digitalis on human coronary vessels deal exclusively with the resistance vessels of the coronary bed.[25,26] In an animal model, Schwartz and Bache[22] demonstrated that intravenous administration of ouaban reduced coronary diameter (measured by sonomicrometry). Between 5 and 10 minutes after ouabain administration external circumflex coronary artery diameter decreased significantly. Ross et al[1] demonstrated that in dogs in which cardiac action was excluded by the use of cardiopulmonary bypass, digitalis caused an increase in peripheral vascular resistance. At a constant perfusion rate, a significant elevation in arterial pressure was not abolished by ganglionic blockade. Vatner et al[2] showed that in conscious dogs, ouabain caused a significantelevation in coronary and systemic resistance with no change in coronary blood flow. Our results demonstrate for the first time that in humans, rapid bolus administration of digoxin produces a decrease in cross-sectional area of normal coronary arteries and a reduction in minimal coronary stenosis diameter in patients with atherosclerotic lesions. In the present study, nitrates were administered sublingually, rather than intracoronary, in order to assess the possible clinical beneficial role of these drugs on digoxin-induced coronary vasoconstriction. Our data indicated that 5 mg of isosorbide dinitrate given sublingually can

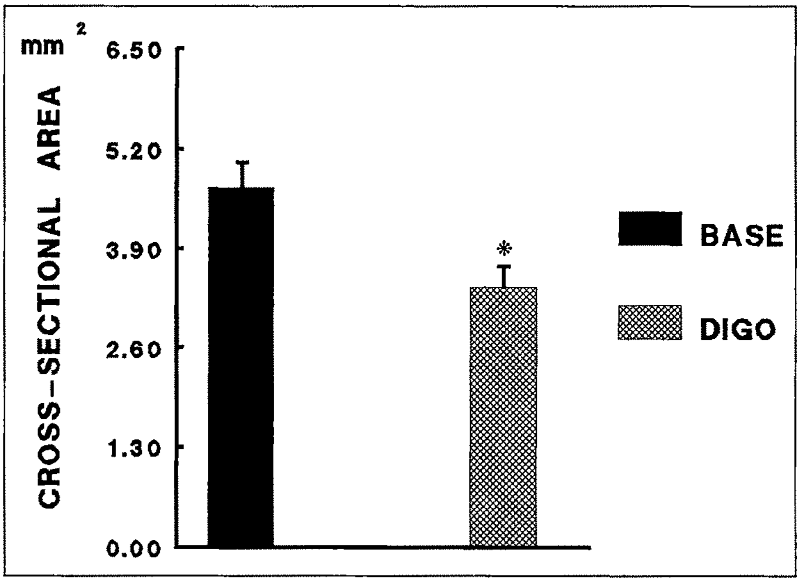

**FIGURE 2. Changes in cross-sectional area in patients with normal coronary arteries pretreated with intravenous phentolamine observed 20 minutes after the end of digoxin (DIGO) infusion. BASE = baseline; *p <0.05 versus control.**

revet the effect of cardiac glycosides on coronary diameter. An experimental study has also shown that nifedipine prevents ouabain-induced coronary vasoconstriction.[27]

Although it has been demonstrated[3,28] that in open-chest anesthetized dogs the effects of digitalis on coronary artery resistance are mediated through an α-adrenergic mechanism, our data demonstrated that the coronary constriction induced by digoxin also occurs when α-adrenrgic receptors are blocked by phentolamine. Therefore, it is unlikely that this constriction was mediated by an α-adrenergic mechanism.

Quantitative analysis of digital angiograms is a reliable and accurate technique for measuring epicardial coronary diameter in man.[8,12,29] In addition, a previous study from our laboratory demonstrated a good reproducibility of serial measurements of the same coronary segmet during repeated contrast injection after the injection of 5 to 8 ml of nonionic contrast medium.[12]

**Clinical relevance:** The finding that digoxin constricts epicardial coronary arteries may have clinical importance. In fact, digitalis is often administered acutely to patients with myocardial infarction as well as to elderly patients without heart failure but with significant coronary artery stenosis who undergo thoracic or cardiac operations. The appearance of ischemic pain described after administration of digoxin in patients with myocardial infarction[30] may also be due to an epicardial coronary vasoconstriction.

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# Usefulness of Ambulatory Silent Myocardial Ischemia Added to the Prognostic Value of Exercise Test Parameters in Predicting Risk of Cardiac Death in Patients with Stable Angina Pectoris and Exercise-Induced Myocardial Ischemia

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**The prognostic significance of ambulatory silent ischemia detected by Holter monitoring during daily life was prospectively evaluated and compared with several exercise test parameters in 86 patients with stable angina and positive exercise tests. Forty-seven patients (group 1) had no evidence of ischemia and 39 (group 2) had 1 or more episodes of silent ischemia during the monitoring period. During mean follow-up of 24 ± 8 months there were only 2 cardiac deaths (nonsudden) in group 1 (4% mortality) compared with 9 (3 sudden and 6 nonsudden) in group 2 (23% mortality). Kaplan-Meier actuarial analysis revealed worse survival ($p < 0.008$) for patients in group 2. The Cox regression analysis of clinical variables, electrocardiographic and exercise parameters, angiographic data and Holter monitoring results revealed silent ischemia during daily life as the most powerful predictor of cardiac mortality ($p = 0.003$). These results demonstrate that in patients with chronic stable angina and abnormal exercise tests, ambulatory ischemia detected by Holter monitoring provides significant additional prognostic information to that derived from evaluation of exercise test parameters alone.**

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Although silent ischemia during daily life occurs far more frequently than anginal symptoms in patients with chronic stable angina, the clinical need for Holter monitoring in these patients has been questioned.[1] This question has been raised because despite the results of recent studies,[2–5] showing an increased risk of coronary events and cardiac death in stable angina patients with ambulatory silent ischemia, the data comparing the prognostic information derived from the exercise test findings with that derived from Holter monitoring are lacking. Such comparative studies are needed because it is well-known that selected exercise test parameters obtained during routine treadmill exercise testing provide reliable and clinically useful prognostic information in patients with stable coronary artery disease.[6–15] In this prospective study we evaluated the prognostic value of ambulatory ischemia detected by Holter monitoring and compared it with that of selected exercise test parameters in patients with stable angina and exercise-induced ischemia.

## METHODS

**Patient selection:** Consecutive male patients participating in our ongoing study on silent ischemia with a clinical diagnosis of coronary artery disease, stable angina for ≥6 months, and exercise-induced ischemia were selected. All patients gave written informed consent that was approved by the hospital's human study and research committees. Coronary artery disease was confirmed by 1 or more of the following: ≥70% luminal narrowing of ≥1 major coronary artery; reversible perfusion defect on exercise thallium-201 scintigraphy; or a myocardial infarction ≥6 months prior to participation in the study. Patients with left bundle branch block, preexcitation, left ventricular hypertrophy, pacemaker rhythms, atrial arrhythmias and other baseline ST changes were excluded. Patients with uncorrected hypokalemia and those receiving digitalis or tricyclic antidepressants were also excluded. Patients continued receiving antianginal drugs prescribed by their primary care physicians at stable dosages for ≥3 months prior to enrollment in the study.

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**Study design:** All patients underwent symptom-limited maximal exercise treadmill testing and 24-hour Holter monitoring while continuing to receive their antianginal drugs. Holter tapes were coded to mask the patients' identities. Exercise treadmill testing was performed by physicians who were unaware of the Holter findings. The results of the Holter monitoring and the exercise tests were analyzed at a later date in a blinded fashion by 2 investigators. To avoid any subsequent deviation from the usual treatment in these patients, the results of Holter monitoring were not made available to the physicians providing primary care. All patients were followed throughout the study at regular 3 to 4 month intervals.

**Treadmill exercise tolerance test:** All patients had a positive ischemic response during exercise defined as ≥1-mm horizontal or downsloping ST depression at 80 ms after the J point. Twelve-lead electrocardiograms were obtained every minute during the exercise and recovery periods, and at onset of ischemia. Exercise duration, time to onset of ischemia, and heart rate and blood pressure at rest, at onset of ischemia and at peak exercise, as well as ST depression and symptoms, were recorded.

**Holter monitoring technique:** The Holter monitoring technique used in our laboratory has been described in detail.[16] In brief, 2-channel Holter recordings for 24 hours were obtained using a frequency modulated recording device (Medilog MR 20, Oxford, England). Anterior precordial and inferior leads matching the leads showing maximal ST depression during the exercise test were selected. Patients were instructed to record the number and duration of angina episodes. An ischemic episode was defined as ≥1 mm horizontal or downsloping ST depression measured 80 ms from the J point, and lasting ≥1 minute. For each patient, the number and duration (minutes) of episodes were determined. An episode was labeled symptomatic or silent based on details recorded in the diary. Holter findings were blindly reviewed by ≥2 experienced investigators.

**Patient follow-up:** The primary purpose of this study was to compare and evaluate the prognostic value of selected exercise test parameters and silent ischemia during Holter monitoring in predicting the risk of cardiac death. However, detailed information was obtained for all clinical events during follow-up. The specific events evaluated included: death due to any cause; myocardial infarction; unstable angina; and need for myocardial revascularization owing to worsening symptoms. Deaths were classified as cardiac (sudden and nonsudden) or noncardiac. Sudden death was defined as death occurring ≤1 hour after the onset of symptoms. The details of death were obtained from relatives, primary care physicians, hospital records, obituaries and coroner's reports. Medical records were reviewed for hospitalized patients. The diagnosis of unstable angina was made by the primary care physician and confirmed by absence of electrocardiographic changes or cardiac enzyme profile indicative of acute myocardial infarction. The decision to recommend myocardial revascularization was made by the primary care physician and was generally based on increasing symptoms refractory to medical therapy, angiographic findings indicative of left main (≥50% obstruction) or 3-vessel disease, with left ventricular ejection fraction <40%.

**Analysis of data:** Comparisons between the groups were performed with an unpaired *t* test of significance for continuous variables, and chi-square analysis was performed for categorical variables. Data are expressed as frequency or mean ± standard deviation for normally distributed and continuous variables, respectively; otherwise, they are reported as median and range. A p value ≤0.05 was considered statistically significant.

Kaplan-Meier actuarial methods[17] were used to examine the time-dependent cumulative probabilities of death and occurrence of nonfatal cardiac events, and differences were evaluated by the method of Mantel-Haenszel.[18] Multivariate Cox's proportional hazard function analyses were used to evaluate the relative importance of clinical variables, electrocardiographic and exercise parameters, and Holter findings. This was done to ensure that our results were not affected by any of these confounding variables.[19] The clinical variables included in the analyses were age, hypertension (>150/90 mm Hg), diabetes, smoking, prior myocardial infarction and presence of Q waves. The exercise variables were exercise duration, time to and heart rate at onset of ischemia, and peak heart rate and blood pressure. The Holter parameter used was presence or absence of ambulatory silent ischemia.

## RESULTS

**Patient population and clinical characteristics:** Eighty-six patients (mean age 63 ± 6 years) with a long history of angina (9.4 ± 7 years) were followed for 24 ± 8 months (range 12 to 31). The study population was divided in 2 groups: Group 1 (n = 47) consisted of patients without ischemia and group 2 (n = 39) included patients with ≥1 ischemic episode during Holter monitoring. Analysis of the clinical characteristics of the 2 groups has been described, and revealed no significant difference.[16] Comparison of the prescribed antianginal drugs revealed no difference between the 2 groups. Comparison of angiographic findings in groups 1 (n = 33) and 2 (n = 29) revealed no significant difference in the extent of coronary artery disease (≥70% narrowing in 1, 2 or 3 vessels; Figure 1). Of 11 patients with left main disease (≥50% narrowing), 10 had prior coronary bypass surgery and 1 (group 1) refused revascularization. The mean left ventricular ejection fraction was not significantly different between the groups (53 vs 49%).

**Exercise test parameters:** Comparison of exercise test parameters revealed that the patients in group 2 had a significantly shorter time to onset of ≥1 mm ST depression (5.0 vs 3.7 min; $p < 0.001$), and a greater degree of ST depression (1.6 ± 0.6 vs 2.0 ± 1.0 mm; $p < 0.01$). The presence of silent ischemia during exercise testing did not predict the risk of silent ischemia during Holter monitoring.

Evaluation of hemodynamic parameters during exercise testing revealed no significant difference be-

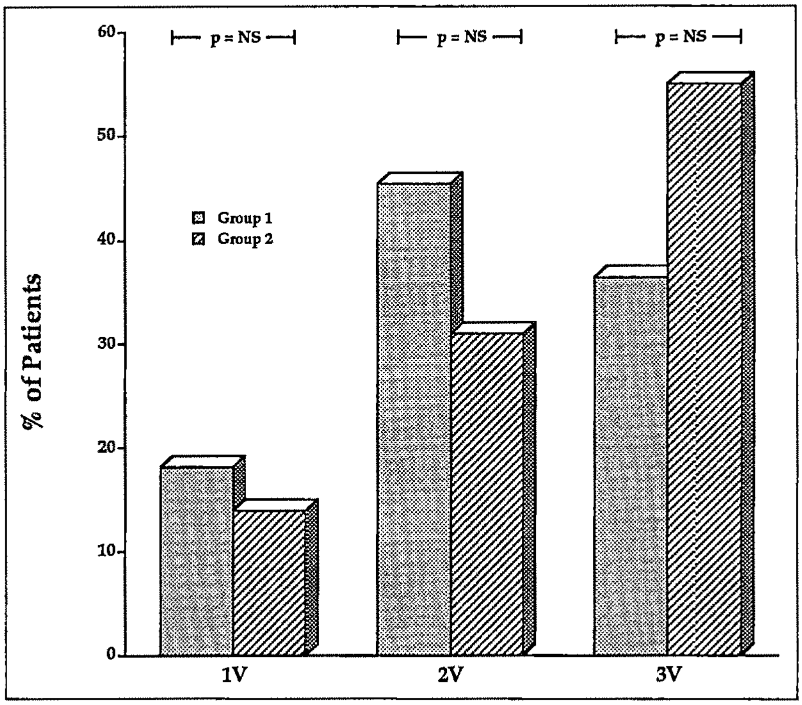

**FIGURE 1. Proportion of patients in group 1 (*dots*) with 1-, 2- or 3-vessel (V) disease compared with that in group 2 (*diagonal lines*). NS = not significant.**

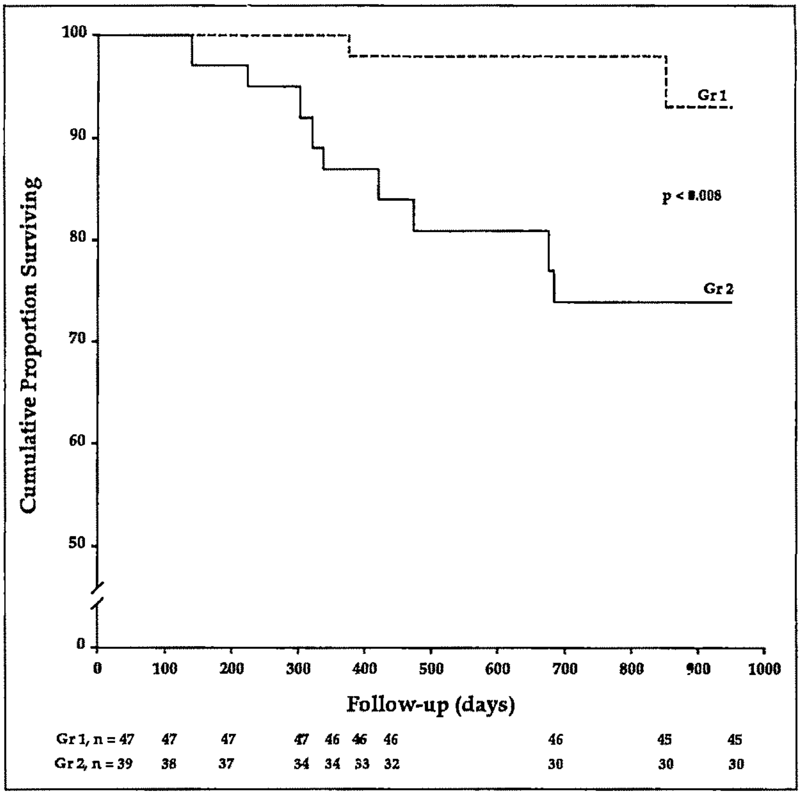

**FIGURE 2. Kaplan-Meier curves comparing cumulative proportion of patients surviving during mean follow-up of 2 years for 47 patients without (group [Gr] 1) and 39 with (group 2) silent ischemia during ambulatory electrocardiographic monitoring ($p < 0.008$). *Numbers at bottom* indicate numbers of patients surviving at corresponding days of follow-up.**

tween the groups in heart rate (107 ± 25 vs 104 ± 21 beats/min) or double product at onset of ischemia (17,900 ± 5,300 vs 15,800 ± 5,500). However, systolic blood pressure at 1-mm ST depression (165 ± 26 vs 151 ± 24 mm Hg; $p < 0.04$), and peak double-product during exercise (224 ± 52 vs 190 ± 62; $p = 0.01$) were significantly lower in patients in group 2.

**Ambulatory electrocardiographic monitoring findings:** During the 2,064 hours of Holter monitoring, 154 ischemic events were recorded in 39 patients (45%). Most ischemic episodes were silent (n = 133, 86%) and accounted for the majority of ischemic time (4,577 minutes, 83%). Although most patients (74%) had silent ischemic events only, 10 (26%) had silent and symptomatic ischemic events. In these 10 patients, the number of silent events (5.8 ± 4.6) was higher than that of symptomatic events (2.1 ± 1.4); however, the duration of silent events (27 ± 18 min) was about half that of symptomatic episodes (55 ± 63 min; p = NS).

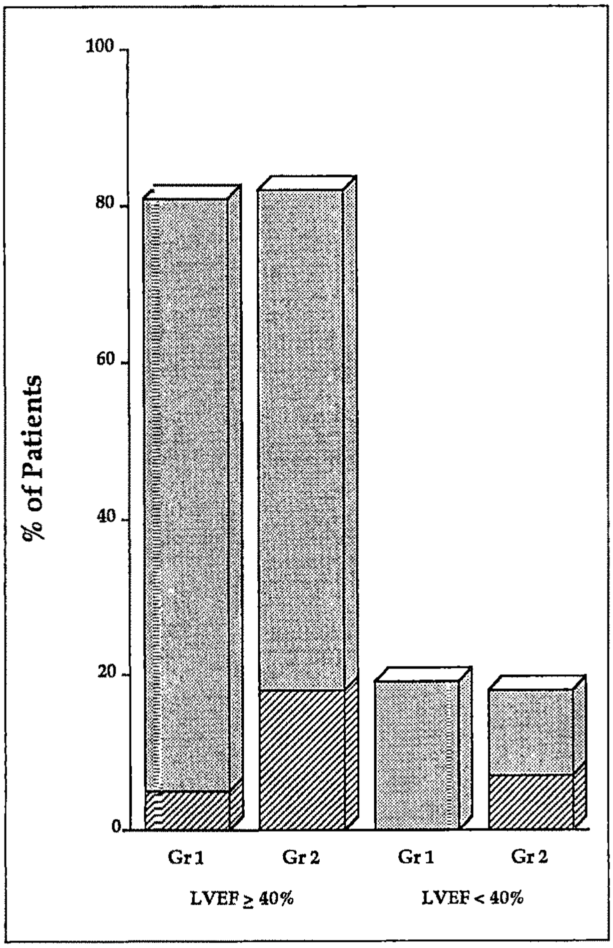

**FIGURE 3. Comparison of left ventricular ejection fraction (LVEF) and cardiac death rate (*diagonal lines*) between patients without (group [Gr] 1) and with (group 2) silent ischemia during ambulatory electrocardiographic monitoring. Although a greater percentage of patients with ambulatory ischemia died there was no significant difference in death rates between patients with LVEF < or ≥40%.**

**Clinical outcome during follow-up:** During 24 ± 8 months of follow-up there were 14 deaths, 3 of which were noncardiac (1 cancer, 1 suicide and 1 gastrointestinal bleed). Because excluding noncardiac deaths did not affect the results, only cardiac deaths will be described in subsequent analyses.

**Ambulatory ischemia and cardiac deaths:** Eleven patients died due to cardiac causes during follow-up. Two of 47 (4%) patients in group 1 died compared with 9 of 39 (23%) in group 2. Both deaths in group 1 were nonsudden and associated with acute myocardial infarction. In contrast, there were 3 sudden and 6 nonsudden cardiac deaths in patients in group 2. All nonsudden cardiac deaths in group 2 were associated with myocardial infarctions.

Kaplan-Meier actuarial analysis revealed a significantly worse survival for patients with silent ischemia during Holter monitoring ($p < 0.008$; Figure 2). At 1 year, survival in group 1 was 100% compared with 87 ± 11% in group 2, and at 2 years it was 98 ± 1 and 74 ± 15%, respectively. Kaplan-Meier survival analysis was repeated after excluding the 16 patients with previous coronary artery bypass surgery. This analysis still revealed a significantly decreased cumulative survival in patients with silent ischemia during Holter monitoring (65 ± 19 vs 97 ± 5% at 2 years; $p < 0.005$). We also evaluated the prognostic significance of duration of silent ischemia and found no significant difference in survival between patients with <60 minutes of silent ischemia per 24 hours of Holter monitoring and those with ≥60 minutes duration. Evaluation of survival patterns between the groups according to left ventricular ejection fraction of ≥ or <40% revealed that patients in both groups with ambulatory ischemia had higher mortality compared with those without ischemia (p = not significant; Figure 3).

**Ambulatory ischemia and nonfatal events:** Kaplan-Meier actuarial analysis of nonfatal acute myocardial infarction, unstable angina and need for myocardial revascularization did not reveal a significant difference between the 2 groups. In group 1, one patient developed a myocardial infarction, 17 had unstable angina and 2 underwent myocardial revascularization compared with 1 myocardial infarction and 14 patients with unstable angina in group 2. Although the median time to a nonfatal cardiac event was shorter (474 vs 851 days) in patients in group 2, this difference was not statistically significant.

**Exercise test parameters and cardiac mortality:** We evaluated the prognostic importance of functional capacity, time to onset of ischemia, and peak heart rate during exercise testing, because these parameters have been shown to provide reliable prognostic information in patients with stable angina.[6-12]

Comparison of survival patterns between the 44 patients with exercise duration <6 minutes and the 42 with duration ≥6 minutes revealed no significant difference in the mortality rates (14 vs 12%). Similarly, comparison of the 70 patients with early onset of exercise-induced ischemia (<6 minutes) with the 16 with late onset (≥6 minutes) did not reveal a significant difference in mortality rates (14 vs 6%). Finally, we evalu-

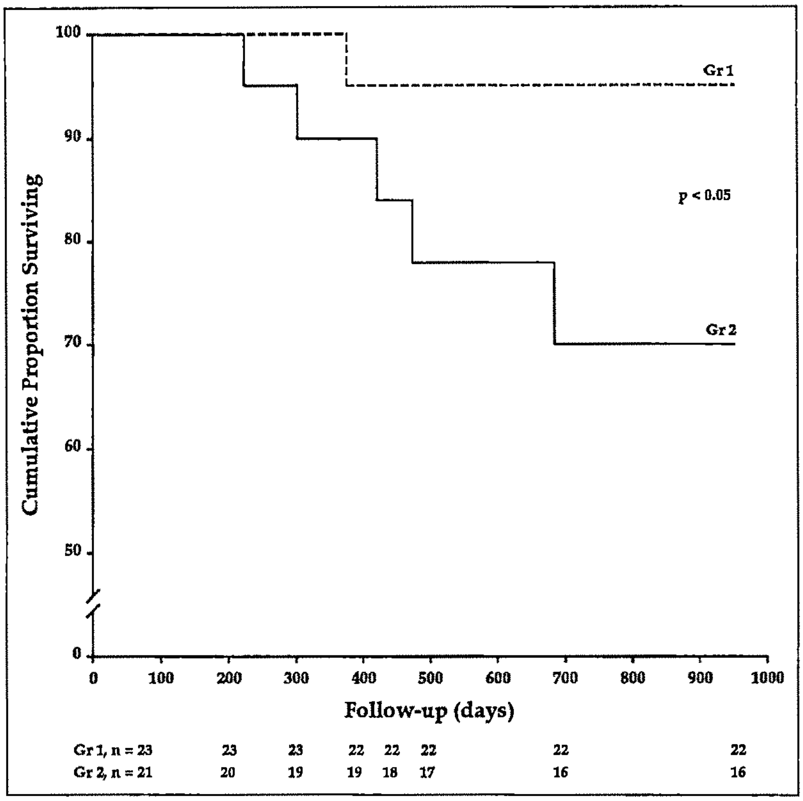

**FIGURE 4. Kaplan-Meier curves comparing cumulative proportion of patients surviving during mean follow-up of 2 years for 44 patients with exercise duration <6 minutes. The 23 patients without silent ischemia (group [Gr] 1) had better survival than the 21 with silent ischemia (group 2) during ambulatory electrocardiographic monitoring (p <0.05).**

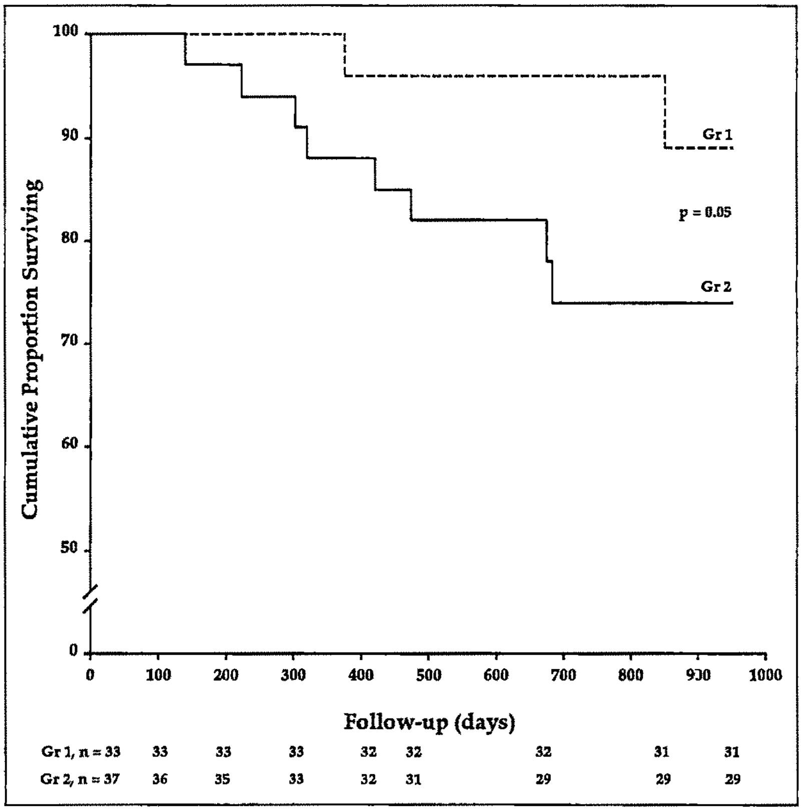

**FIGURE 5. Actuarial survival curves comparing cumulative proportion of patients surviving during mean follow-up of 2 years for 70 patients with early (within second stage of Bruce protocol) ischemic response during exercise test. Patients without silent ischemia (group [Gr] 1) had better survival than those with silent ischemia (group 2) during ambulatory electrocardiographic monitoring (p = 0.05).**

ated survival in patients with peak exercise heart rates <120 (n = 41, 20% mortality) or ≥120 (n = 41, 5%) beats/min. We found a significantly worse prognosis in patients with peak heart rates <120 beats/min (p = 0.05).

**Additional prognostic value of ambulatory silent ischemia:** To evaluate the additional predictive value of ambulatory silent ischemia in defining the risk of cardiac death, we compared the cumulative survival based on selected exercise test parameters and presence or absence of silent ischemia during Holter monitoring. In patients with reduced exercise capacity (<6 minutes), ambulatory silent ischemia identified the group at increased risk of cardiac death (p <0.05; Figure 4). Among patients with exercise duration ≥6 minutes there was a worse prognosis for those with silent ischemia during Holter monitoring; however, it reached only marginal significance (p = 0.09).

The presence of ambulatory ischemia also helped in further stratification of patients with early onset of exercise-induced ischemia (<6 minutes). In this subset those with ambulatory ischemia had a significantly worse survival (p = 0.05; Figure 5).

In addition, we evaluated the prognostic significance of ambulatory silent ischemia in patients with peak exercise heart rates ≥ or <120 beats/min. In patients with peak exercise heart rates ≥120 beats/min, the presence of ambulatory ischemia was associated with a significantly higher mortality (p = 0.03; Figure 6, top panel). Although the mortality rate was higher in

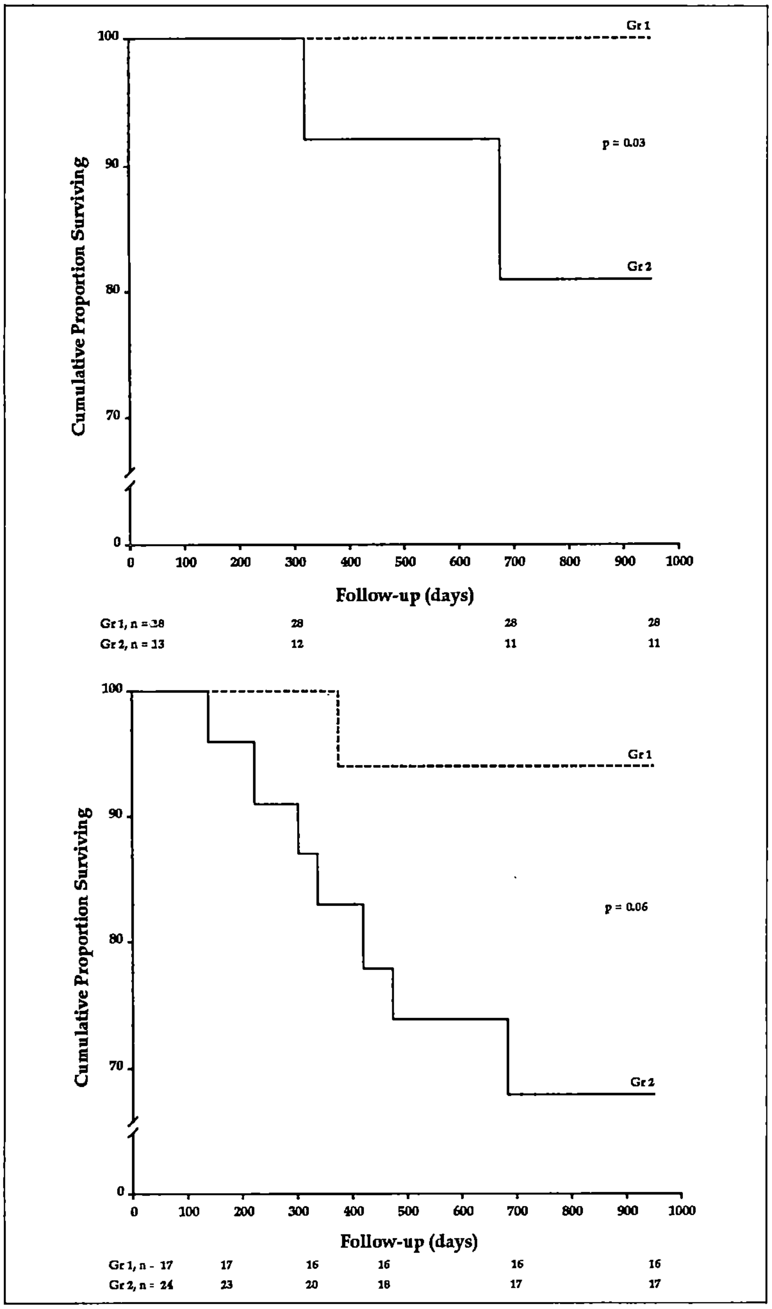

**FIGURE 6. Kaplan-Meier curves comparing survival patterns in subgroups of patient based on peak exercise heart rate < or ≥120 beats/min. *Top panel* shows that for patients (n = 41) with peak heart rates ≥120 beats/min, those without silent ischemia (group [Gr] 1; n = 28) had better survival than those with ambulatory silent ischemia (group 2; n = 13; p = 0.03). *Bottom panel,* survival pattern for patients with peak heart rates <120 beats/min. Although mortality was higher for group 2 (n = 24) than for 1 (n = 17), the difference in mortality reached only marginal significance (p = 0.06).**

the 24 patients with peak exercise heart rates <120 beats/min and ambulatory silent ischemia (29%) than in the 17 with peak exercise heart rates <120 and without ischemia (6%), this difference only reached marginal significance ($p = 0.06$; Figure 6, bottom panel).

**Multivariate Cox's regression analysis:** Cox's multivariate proportional hazard function analyses were performed to determine the relative importance of Holter monitoring findings, clinical variables, electrocardiographic abnormalities, exercise test results and angiographic data in predicting 2-year cardiac mortality. On the initial Cox's hazard function analysis, the presence of ambulatory silent ischemia was found to be the most significant predictor of 2-year cardiac mortality ($p = 0.0001$). The other variables (in decreasing order of importance) were heart rate at onset of exercise-induced ischemia ($p = 0.004$), peak heart rate during exercise ($p = 0.005$), exercise duration ($p = 0.007$), time to onset of exercise-induced ischemia ($p = 0.007$), and active cigarette smoking ($p = 0.03$). The remaining variables did not provide any additional prognostic information.

Multivariate Cox's hazard function analysis was repeated after excluding Holter monitoring data. In this analysis, the only significant predictors of cardiac death were heart rate at onset of exercise-induced ischemia ($p < 0.01$) and peak heart rate during exercise ($p < 0.02$). In the next step, Holter monitoring data were added to the model. This improved the predictive value of the model and revealed ambulatory silent ischemia during Holter monitoring as the most important and independent ($p = 0.003$) predictor of cardiac mortality. The other significant predictors were peak heart rate during exercise ($p = 0.004$) and heart rate at onset of exercise-induced ischemia ($p = 0.008$).

Finally, Cox's regression analysis was repeated allowing the model to determine the most important variables in predicting cardiac mortality. This analysis revealed presence of ambulatory ischemia as the most powerful ($p < 0.001$) predictor followed by exercise duration ($p < 0.01$), time to onset of exercise-induced ischemia ($p < 0.02$), and hypertension ($p = 0.04$) as the other significant predictors of cardiac death.

## DISCUSSION

These results show that presence of silent ischemia detected by Holter monitoring performed during daily life provides significant additional and independent prognostic information to that available from the exercise test parameters in patients with stable angina and a positive exercise test.

**Prognostic value of Holter findings versus exercise test parameters:** Previous studies in patients with stable coronary artery disease have demonstrated that transient ischemic events, mostly silent, occur frequently during daily life.[1,2,5,20,21] Our results confirm these findings and show that most ischemic events during daily life are silent and account for a majority of the total ischemic time. One important difference between previous reports and our study is that ambulatory ischemia was present in our patients despite control of anginal symptoms.

Exercise testing is routinely performed and provides important prognostic information in patients with coronary artery disease.[6–15] Direct comparison between the prognostic value of Holter findings and exercise test parameters in our study revealed that in patients with reduced exercise capacity, presence of silent ischemia during daily life further stratifies patients who are at higher risk of cardiac death (Figure 4). Similarly, ambulatory silent ischemia provided additional prognostic information in patients with an early ischemic response during exercise testing (Figure 5). In patients with lower peak exercise heart rate (<120 beats/min), the presence of ambulatory silent ischemia provided only marginal additional prognostic information, but did identify the subgroup at increased risk of cardiac death in patients with higher peak exercise heart rates (≥120 beats/min; Figure 6). Finally, multiple logistic regression analysis revealed presence of ambulatory silent ischemia as the most important and independent predictor of cardiac mortality.

**Clinical importance of findings:** The results of this study provide clinically relevant and useful information. Our findings demonstrate that ambulatory ischemia that is predominantly silent occurs frequently in patients with stable angina despite control of symptoms with antianginal drugs. Although it is generally accepted that selected exercise test parameters provide reliable prognostic information, our results show that presence of ambulatory ischemia detected by Holter monitoring provides significant additional and independent prognostic information in patients with chronic stable angina and exercise-induced ischemia.

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# Usefulness of Electrocardiographic Findings and Creatine Kinase Levels on Admission in Predicting the Accuracy of the Interval Between Onset of Chest Pain of Acute Myocardial Infarction and Initiation of Thrombolytic Therapy

Aernout M. Beek, MD, Freek W. A. Verheugt, MD, and Albert Meyer, MD

**Patients with chest pain lasting >6 hours and suggesting acute myocardial infarction (AMI) are often excluded from thrombolytic therapy, because myocardial necrosis is believed to be largely irreversible beyond that time. To evaluate the relation between time of onset of chest pain and enzymatic evidence of myocardial necrosis, enzymes on admission were analyzed in 221 consecutive patients with ≥2 mm ST-segment elevation by electrocardiography on admission and no contraindications to thrombolytic therapy. Patients with symptoms within 6 hours (n = 170, early) received thrombolytic therapy, but those with symptoms after 6 hours did not (n = 51, late). Eventually, 219 (168 early, 51 late) patients had enzymatically proven AMI within 24 hours. Creatine kinase levels on admission less than twice the upper normal limit were found in 155 (91%) early patients, but surprisingly, also in 30 (59%) late patients. By electrocardiography on admission, ST-segment elevation per lead was 2.1 ± 1.1 mm in late patients with low initial enzymes versus 1.1 ± 0.3 mm in those with elevated initial enzymes ($p < 0.0001$). Concomitantly, Q waves in leads with ST-segment elevation were present in 17 (57%) late patients with low enzymes on admission versus 17 (81%) with elevated enzymes on admission ($p = 0.06$). Eventually, maximal creatine kinase levels were similar in all late patients irrespective of enzyme levels on admission. Therefore, many patients with symptoms of AMI after 6 hours have low enzymes on admission and may still be eligible for thrombolytic therapy. Immediate enzyme testing and the degree of ST-segment elevation by electrocardiography on admission may identify these patients. These data could explain the improved survival reported with "late" thrombolytic therapy for AMI.**

**(Am J Cardiol 1991;68:1287–1290)**

Thrombolysis is a fully accepted and well-established therapy for acute myocardial infarction (AMI). To gain maximal benefit it is essential that therapy is instituted as early as possible. The large Gruppo Italiano Per Lo Studio Della Streptochinasi Nell'Infarcto Miocardico-1 (GISSI-1) study[1] only showed statistically significant benefit when thrombolysis was accomplished within 6 hours after onset of the first symptoms. After a longer period of ischemia, the unperfused myocardial tissue was thought to be damaged beyond repair, and reperfusion was no longer thought to have any effect on myocardial salvage. However, some earlier small studies[2] and the very large Second International Study of Infarct Survival (ISIS-2) trial[3] demonstrated that thrombolysis may be effective in improving survival for a period up to 24 hours. A recent meta-analysis of 67 published trials[4] suggested, by logistic regression analysis, mortality reduction up to 21 hours after onset of the first symptoms. However, an explanation for these findings has never been given.

It could be that the myocardial cell in humans is capable of retaining its viability for a longer period of time than in animal models. However, the period of ischemia leading to irreversible damage might not be as long, as can be inferred from the duration of symptoms. Due to intermittent coronary occlusion, the patient could have unstable prodromal angina pectoris before the actual infarction occurs, which might overestimate the duration of infarction. Several studies with and without thrombolytic therapy have shown a strong relation between symptom onset and the development of AMI, using enzymatic[5,6] and angiographic[7] methods. However, the patient's history is a subjective way of assessing the duration of AMI, and its reliability can be questioned.

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**TABLE I** Demographic and Clinical Data of Patients Arriving Later Than Six Hours After Onset of Symptoms of Acute Myocardial Infarction

| | Creatine Kinase Level on Admission | |
|---|---|---|
| | <250 U/liter (%) | >250 U/liter (%) |
| No. of pts. | 30 | 21 |
| Men (%) | 55 | 77 |
| Age ± SD (yrs) | 65 ± 7 | 61 ± 8 |
| Age range (yrs) | 40–74 | 41–75 |
| History of infarction | 4 (13) | 4 (19) |
| History of cigarette smoking | 11 (37) | 12 (57) |
| Family history of CAD | 10 (33) | 4 (19) |
| History of systemic hypertension | 11 (37) | 5 (24) |
| History of diabetes mellitus | 3 (10) | 2 (10) |
| History of angina pectoris | 1 (3) | 0 (0) |
| History of hypercholesterolemia | 0 (0) | 1 (5) |
| Use of aspirin | 1 (3) | 0 (0) |
| Use of β blockers | 2 (7) | 4 (19) |

CAD = coronary artery disease; SD = standard deviation.

In this study we compared the duration of symptoms with both creatine kinase levels and electrocardiography on admission in a large group of patients with AMI eligible for thrombolysis. The main goal of this descriptive study was to test the reliability of symptom duration according to the history of the patient in relation to creatine kinase levels and electrocardiography on admission.

## METHODS

Between January 1, 1988, and December 31, 1989, 221 consecutive patients aged <75 years were admitted to our hospital with: (1) continuous chest pain >30 minutes; (2) ≥2 mm ST-segment elevation in ≥2 contiguous leads by electrocardiography; and (3) no contraindications to thrombolysis. Physical examination, history and interpretation of electrocardiography on admission were performed in the emergency room by a cardiology fellow supervised by an experienced cardiologist.

Patients with duration of symptoms <6 hours received 1.5 million U of streptokinase intravenously over 30 minutes in the emergency department according to our protocol.[8] Those with symptom duration >6 hours did not receive thrombolytic therapy. Development of AMI was defined by an increase within 24 hours of creatine kinase, aspartate aminotransferase and lactate dehydrogenase to more than twice the upper normal limits. Enzymes were determined on admission, 6 hours later and, subsequently, every 12 hours until the fourth hospital day.

In all patients, creatine kinase levels on admission were available for analysis (Technicon EC 2.7.3.2., Tarrytown, New York). In our institution, the coefficient of the variation of reproducibility at 100 U/liter and 30°C is 5.0% in duplicate.

**TABLE II** Duration of Symptoms and Creatine Kinase Levels on Admission in Patients Arriving Later Than Six Hours After Onset of Symptoms of Acute Myocardial Infarction

| | Creatine Kinase Level on Admission | |
|---|---|---|
| | <250 U/liter | >250 U/liter |
| No. of pts. | 30 | 21 |
| Duration of symptoms, mean ± SD (hrs) | 13 ± 14 | 15 ± 7 |
| Duration of symptoms, <24 hours (n) | 27 (90%) | 19 (86%) |
| Creatine kinase on admission | | |
| Median (U/liter) | 121 | 842 |
| Range (U/liter) | 38–241 | 295–2,228 |
| Maximal creatine kinase | | |
| Median (U/liter) | 888 | 892 |
| Range (U/liter) | 292–2,525 | 295–2,228 |

SD = standard deviation.

According to data published earlier,[7] the duration of AMI was considered to have been >6 hours when creatine kinase level on admission was >250 U/liter, which is twice the upper normal limit in our institution. AMI was thought to have lasted <6 hours when creatine kinase level was <250 U/liter on admission.

First, we examined the relation between duration of symptoms and creatine kinase levels on admission. Second, the electrocardiographic features of transmural AMI in patients with symptoms after 6 hours were reviewed and analyzed by 2 experienced cardiologists. ST-segment elevation was measured and Q waves were scored only in the leads with ST-segment elevation. Q waves were considered to be pathologic when the duration was ≥40 ms and the amplitude was ≥25% of the ensuing R wave. No interobserver variability between the 2 cardiologists was noted.

**Statistical analysis:** Comparisons of frequency distribution between groups were performed with the chi-square test. The Student *t* test was used to compare continuous variables between groups. Two-sided p values are given.

## RESULTS

**Early patients:** In our institution, 77% (170 of 221) of the patients presenting with symptoms and electrocardiographic signs of AMI, and eligible for thrombolysis arrived within 6 hours after onset of symptoms and received thrombolytic therapy. Two patients (1%) did not develop AMI by the aforementioned enzymatic criteria within 24 hours after admission and were not included in this analysis.

**Late patients:** Fifty-one patients (23%) were admitted >6 hours after onset of symptoms and were not treated with thrombolytic therapy. Surprisingly, 30 patients (59%) arriving late had admission creatine kinase levels <250 U/liter, and 21 (41%) had levels >250 U/liter. There were no significant differences between late patients with and without elevated enzyme levels on admission in the demographic and clinical data (Table I). Unstable anginal symptoms occurred in only 1 patient (in the group with low enzymes on admission) before the final symptoms began. The eventual peak enzyme level was similar in patients with both normal and elevated enzyme levels on admission (Table II). Most patients arriving >6 hours after onset of symptoms did so within 24 hours. The electrocardiographic characteristics in relation to the enzyme levels on admission are listed in Table III (Figure 1). Patients with positive enzymes tended to have less ST-segment elevation and more pathologic Q waves. However, there is a considerable overlap, and the difference in the trend observed is not statistically significant.

**TABLE III** Electrocardiography on Admission in Patients Arriving Later Than Six Hours After Onset of Symptoms of Acute Myocardial Infarction

| | Creatine Kinase Level on Admission | | |
|---|---|---|---|
| | <250 U/liter | >250 U/liter | p Value |
| No. of pts. | 30 | 21 | |
| Pts. with pathologic Q waves | 17 (57%) | 17 (81%) | 0.06 |
| ST-segment elevation per patient, mean ± SD (mm) | 7.6 ± 4.8 | 3.7 ± 1.6 | 0.001 |
| ST-segment elevation per lead, mean ± SD (mm) | 2.1 ± 1.1 | 1.1 ± 0.3 | 0.0001 |

SD = standard deviation.

## DISCUSSION

This study clearly shows that a high proportion of patients presenting late (>6 hours after onset of pain) with symptoms and signs of AMI have creatine kinase levels that are within twice the upper normal limit. These data suggest that history of onset of symptoms may not be reliable in judging eligibility for thrombolytic therapy. Furthermore, the electrocardiographic findings in these patients suggest that myocardial necrosis may not yet be fully in progress. Eventually, they develop peak enzyme levels of the same magnitude as those of patients arriving late who already had elevated enzymes on admission.

In this study, 2 cutoff points were used: 6 hours after onset of pain; and twice the upper normal limit of creatine kinase. The time limit of 6 hours was chosen because it is used in most thrombolytic protocols and, also, because it has been shown that after 6 hours of coronary occlusion, myocardial enzymes in humans are elevated.[7] We used an arbitrary and rather high cutoff point of twice the upper normal limit of creatine kinase to discriminate between new and developing AMI. All patients admitted late in this study with creatine kinase levels on admission that were within normal range (<125 U/liter) had electrocardiographic signs of transmural ischemia (ST elevation) that were greater than in patients with enzymes >125 U/liter (Figure 1). In the large Multicenter Investigation of Limitation of Infarct Size (MILIS),[6] creatine kinase-MB was elevated 4 hours after onset of pain. Because creatine kinase peaks later than creatine kinase-MB, it is very likely that creatine kinase would be elevated 6 hours after onset of pain.

The basis of our findings is unclear. It could be that patients with low enzymes on admission have enzyme kinetics different from those with elevated enzymes. The electrocardiographic findings make this hypothesis unlikely, but do not exclude it. Intermittent coronary occlusion may be another explanation for the discrepancy of symptom duration and low enzymes on admission. In patients with continuous chest pain, intermittent coronary occlusion has been observed.[9] This may

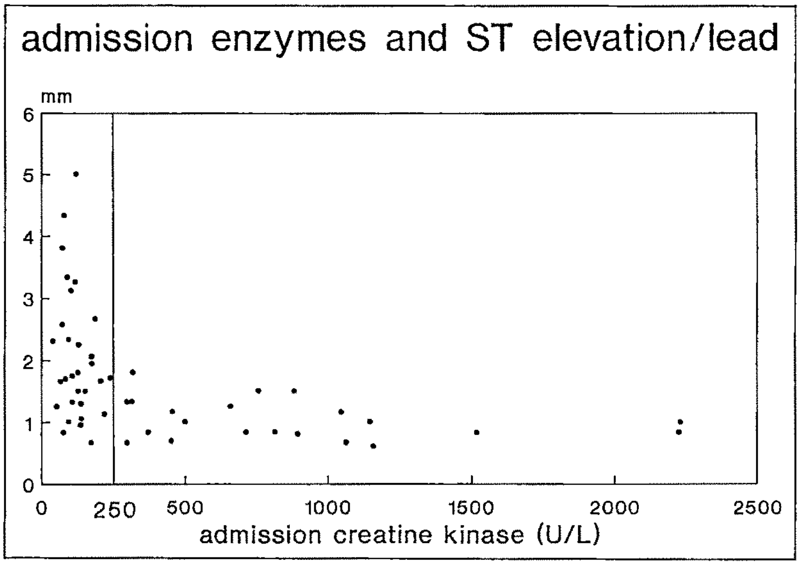

**FIGURE 1. Distribution of mean ST-segment elevation per lead with ST elevation in relation to creatine kinase levels on admission in patients admitted >6 hours after onset of symptoms of acute myocardial infarction.**

herald persistent occlusion leading to AMI.[10] Finally, the presence of collateral circulation may protect against a rapidly developing AMI in some patients.[11]

These findings could have implications for use of thrombolytic therapy for AMI. Most thrombolytic protocols do not include patients admitted >6 hours after onset of symptoms. As suggested by GISSI-1,[1] many clinicians believe that myocardial salvage does not result from late thrombolysis and that only the side effects of thrombolysis will appear in these patients. Patients with symptoms lasting over 6 hours and with low enzymes may benefit from thrombolysis and can be easily identified by early enzyme testing. However, in many emergency departments, immediate enzyme measurements are not available. Electrocardiography on admission can give another clue to the identification of this type of patient. In this study we found that these patients have greater ST-segment elevation and fewer Q waves than patients with elevated enzymes. However, the overlap between the patient groups was considerable, so that clear electrocardiographic guidelines for the identification of patients with low enzymes cannot be obtained from our data.

Although the clinical implications of our findings are probably limited, they may partly explain the remarkable results of late thrombolysis in ISIS-2.[3] In that study, a statistically significant 15% improvement of survival by thrombolysis >6 hours after onset of symptom was demonstrated. Furthermore, a few other smaller studies have shown a similar benefit in patients treated >6 hours after onset of symptoms.[12-14] If we extrapolate our findings in a small group of patients to ISIS-2 it may be that half of the latter patients arriving >6 hours after onset of symptoms had low enzymes on admission and could have the same benefit from thrombolysis as those admitted early in whom improvement of survival was nearly 30%. A major difference between ISIS-2 and our study is that our patients all had confirmed AMI within 24 hours of admission. A major similarity is that both studies analyzed the results in retrospect. The implications of our findings and the definite proof of benefit in patients admitted late can only be established in large prospective controlled mortality trials on "late" thrombolysis. These studies are currently being performed by several investigative groups.[15]

The decision to treat a patient with AMI with thrombolytic therapy has strong prognostic implications and is largely based on subjective data such as history of duration of symptoms. We found an unexplained discrepancy between symptom duration and enzymes on admission, that could cause the attending physician to withhold thrombolysis. To circumvent the subjective steps in the decision tree of thrombolysis, only immediate enzyme testing and electrocardiography are available, which, however, have logistic and discriminative shortcomings.

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# Frequency of Use of Thrombolytic Therapy in Acute Myocardial Infarction in Israel

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**Thrombolysis is now generally accepted as the initial treatment for patients with acute myocardial infarction (AMI). The extent to which this therapy is implemented in daily practice and the reasons for exclusion from thrombolytic therapy among 413 consecutive patients with AMI hospitalized in 18 coronary care units in Israel during a 1-month survey were prospectively investigated. Thrombolytic therapy administered to 145 patients (35%) was given to 38% of men versus 29% of women (p = not significant), to 38% of patients <75 years old compared with 18% of the very elderly (p <0.005), and more often to patients with a first or anterior AMI (40 and 48%) than to counterparts with recurrent or inferior AMI (23 and 31%, respectively, p <0.005 for both). The 2 most frequent reasons for excluding patients from thrombolysis were late arrivals to coronary care units (33%) and lack of ST elevation on the admission electrocardiogram (28%). Hospital mortality was 6% in the thrombolytic group versus 20% in patients found ineligible for thrombolysis. The significance of this difference is not clear as treatment was not randomized.**

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Based on multiple large-scale positive clinical trials it is now accepted that thrombolysis should be the initial treatment for patients with acute myocardial infarction (AMI) without specific contraindications.[1-5] To what extent this salutary therapy is implemented in daily practice has not been sufficiently assessed.[6,7] We investigated the incidence of treatment and the reasons for ineligibility for thrombolytic therapy of patients with AMI hospitalized in 18 of the 23 coronary care units functioning in Israel in early 1990.

## METHODS

A questionnaire was completed in the coronary care unit for each patient with AMI hospitalized in January 1990, irrespective of the administration of thrombolytic therapy. Data recorded were: age, gender, time of pain onset, time until admission to coronary care units, history of previous AMI, AMI site and the following specific reasons for not giving thrombolytic treatment: old age, late arrival, lack of electrocardiographic criteria and contraindication to thrombolysis (see later). The diagnosis of AMI was based on typical chest pain, characteristic electrocardiographic changes and high serum levels of cardiac enzymes (creatinine kinase-MB+, glutamic oxalotransaminase, lactic dehydrogenase). The admission electrocardiogram and the patients charts were not centrally reviewed because the survey was not designed to evaluate the diagnostic accuracy of the participating coronary care units. In-hospital mortality was recorded for all patients with AMI.

There were no uniform guidelines for thrombolytic treatment in the different centers during the survey. However, all the coronary care units had participated in the International Alteplase/Streptokinase study[8] which determined the treatment policy in the coronary care units during the survey period. According to this study protocol patients eligible for thrombolytic therapy had to have typical chest pain lasting between 30 minutes and 6 hours, unrelieved by sublingual nitrates, with an electrocardiogram showing ST-segment elevation of ≥0.1 mV in ≥2 contiguous chest leads, or in leads I or

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*See Appendix for participating centers and investigators of the Israel Society for the Prevention of Heart Attacks.

**TABLE I** Incidence of Thrombolytic Treatment by Gender and Age

| | Thrombolytic Treatment | | | |
|---|---|---|---|---|
| | Total No. of Pts. | No. of Pts. Treated | % | p Value |
| Men | 294 | 111 | 38 | NS |
| Women | 119 | 34 | 29 | NS |
| Age (years) | | | | <0.005 |
| ≤75 | 353 | 134 | 38 | |
| >75 | 60 | 11 | 18 | |
| History | | | | <0.005 |
| First AMI | 292 | 117 | 40 | |
| Recurrent AMI | 121 | 28 | 23 | |
| Type of AMI | | | | <0.005 |
| Q-wave | 369 | 143 | 39 | |
| Non-Q-wave | 44 | 2 | 5 | |
| Location of AMI | | | | <0.005 |
| Anterior | 183 | 88 | 48 | |
| Inferior | 163 | 51 | 31 | |
| Lateral | 23 | 4 | 17 | |
| Total | 413 | 145 | 35 | |

AMI = acute myocardial infarction; NS = not significant.

**TABLE II** Hospital Mortality

| | Thrombolytic Treatment | | | | |
|---|---|---|---|---|---|
| | Yes (n = 145) | | No (n = 268) | | |
| | No. | % | No. | % | p Value |
| Men | 7/111 | 6 | 31/183 | 17 | <0.01 |
| Women | 1/34 | 3 | 22/85 | 26 | <0.01 |
| Age (years) | | | | | |
| ≤75 | 7/134 | 5 | 36/218 | 17 | <0.001 |
| >75 | 1/11 | 9 | 16/49 | 33 | NS |
| Past AMI | | | | | |
| Yes | 3/28 | 11 | 23/93 | 25 | NS |
| No | 5/117 | 4 | 30/175 | 17 | <0.001 |
| Index AMI | | | | | |
| Non-Q-wave | 0/2 | — | 4/42 | 10 | NS |
| Q-wave | 8/142 | 6 | 49/226 | 22 | <0.0001 |
| Anterior | 7/89 | 8 | 20/97 | 21 | <0.001 |
| Inferior | 3/54 | 6 | 26/119 | 22 | <0.001 |
| All patients | 8 | 6 | 53 | 20 | <0.005 |

AMI = acute myocardial infarction; NS = not significant.

aVL, or in 2 of the 3 inferior leads (II, III, aVF); patients also had to be free of the usual reasons for omitting thrombolytic treatment (age >75 years, late arrival to coronary care unit >6 hours, absence of ST elevation on the admission electrocardiogram, excessive systemic hypertension, major surgery or coronary aortobypass grafting within 3 months, history of cerebrovascular accident and recent cardiopulmonary resuscitation). However, each center was free to deviate from these reasons for withholding thrombolytic therapy. Of the 18 participating coronary care units only 4 centers considered age >75 years as contraindication to thrombolysis, whereas only 2 centers did not insist on ST elevation on the admission electrocardiogram for commencement of treatment. Sixteen centers did not provide thrombolysis if patients arrived >6 hours from pain onset.

**Statistical analysis:** Chi-square and *t* tests were used to determine the significance of the differences between proportions and means, respectively. All tests were 2-tailed.

## RESULTS

In January 1990, 413 patients with AMI were hospitalized in the 18 participating coronary care units. Thrombolytic therapy was provided to 145 patients (35%). One hundred thirty-six patients were treated with streptokinase and 9 with tissue plasminogen activator. The use of thrombolytic therapy varied significantly according to different demographic and clinical parameters (Table I). The mean age of patients treated with thrombolysis was 59.2 years versus 65.1 years in the untreated group (p <0.01). Thrombolytic therapy was administered to 38% of men versus 29% of women (p = not significant), to 38% of patients <75 years versus 18% of those >75 years (p <0.005), to 40% of patients with a first AMI versus 23% of those with recurrent AMI (p <0.005), and more often to patients with an anterior (48%) than an inferior (31%) AMI (p <0.005). Mean time from pain onset to institution of treatment was 3.3 hours. Eighty-five percent of the patients were treated within 2 hours of pain onset, 11% between 2 to 6 hours, and only 6 patients were treated later than 6 hours after pain onset. Nineteen patients (13%) received thrombolytic therapy before admission to the coronary care unit (in the ambulance or in the emergency department).

Cardiac catheterization, coronary angioplasty and coronary artery bypass grafting were equally performed in both groups (data not shown). Hospital mortality by gender, age group, AMI in the past and type of AMI, is given in Table II. Hospital mortality was higher among patients not receiving thrombolytic therapy in most subgroups.

Two hundred and sixty-eight patients (65%) were ineligible for thrombolytic therapy, of which 30% were excluded for more than one reason. The 2 most frequent reasons for excluding patients from thrombolytic therapy in this survey were late arrivals to the coronary care unit (33%) and lack of ST elevation on the admission electrocardiogram (28%) (Table III). Analysis of the reasons for excluding patients from thrombolysis in different subsets of patients showed that most (30 of 42) patients with a non-Q-wave AMI were not given thrombolytic therapy because of lack of ST elevation on the admission electrocardiogram. In other subgroups, including patients with a recurrent AMI, late arrival was the principal reason for ineligibility.

## DISCUSSION

**Frequency of thrombolytic therapy:** In 2 large-scale clinical trials,[5,9] the rate of randomized patients to thrombolysis was 37 and 22%, respectively. Lee et al[6] estimated that only 15% of patients with AMI in the USA are potential candidates for thrombolytic therapy. In a recent review, Grines and Demaria[7] estimate that available data suggest that only 10% of patients with infarction in the USA receive thrombolytic drugs.

In a recent publication, Althouse et al[10] reported their experience in 8 hospitals in the Seattle-Tacoma, Washington metropolitan area on the proportion of patients with AMI (n = 1,028) who were eligible for thrombolytic therapy. Twenty-two percent of patients were eligible for thrombolysis but only 179 patients (17%) were actually given thrombolytic therapy.

To the best of our knowledge, our study is the first nationwide survey designed prospectively to assess (1) the percentage of patients with AMI treated with a thrombolytic agent, and (2) the reasons for exclusion. In this survey, 35% of patients admitted to coronary care units with AMI were treated with thrombolysis. This relatively high percentage of patients with AMI treated with thrombolytic agents results partly from the inclusion of some very elderly patients (>75 years) who are no longer routinely excluded from thrombolysis.[5] If 11 patients aged >75 years and 6 patients with symptoms beyond 6 hours who were treated are omitted, the use of thrombolytic therapy is reduced to only 30%. The survey showed that men with AMI received thrombolytic therapy more often than women, although the difference was not statistically significant, and that the use of thrombolytic therapy among patients with a recurrent AMI was significantly lower than that in patients with a first AMI, despite the fact that the former are at increased risk. This latter finding is in accordance with the study of White et al[11] in which patients with new onset of ischemic heart disease (first AMI) were more likely to receive thrombolytic therapy (11%) than patients with a history of chronic ischemic disease (5%, $p < 0.0001$).

**Exclusion from thrombolytic therapy:** The principal reason for ineligibility in this survey was, as in other studies,[12] late arrivals to coronary care units. This is a crucial issue since both in the Italian Group for the Study of Streptokinase in Myocardial Infarction (GISSI)[5] and Second International Study of Infarct Survival (ISIS-2)[4] trials, the degree of reduction of mortality using intravenous streptokinase was strongly related to the lack of delay from onset of pain to treatment. Delay in hospital arrival may be due to patients delaying calls for emergency aid, to logistic problems of patient transportation or to prolonged stay in the emergency ward. In our country a delay in patient transportation is not a critical problem because the national system enables mobile coronary care units to reach the nearest hospital within 1 hour from the patient's call.

**TABLE III** Reasons for Excluding Patients from Thrombolytic Treatment

| | No. of Pts. | % of Excluded |
|---|---|---|
| Age >75 years | 16 | 6 |
| Late arrival to coronary care unit | 89 | 33 |
| Absence of ST elevation on the admission electrocardiogram | 76 | 28 |
| Contraindications to thrombolytic treatment | 61 | 23 |
| Atypical clinical presentation | 7 | 3 |
| Unspecified cause | 19 | 7 |
| Total | 268 | 100 |

The second important reason for excluding patients from thrombolysis in this survey was the absence of ST elevation on the admission electrocardiogram. This was the reason for the exclusion of most patients with a non-Q-wave AMI. In the GISSI study[5] the mortality rate of patients with ST depression was 20.5% in the streptokinase group versus 16.3% in the control group (p = not significant). In the ISIS-2 study,[4] mortality in patients with ST depression was not affected by streptokinase (18.7%) compared with the placebo group (18.0%).

The difference in hospital mortality between the group of patients who received thrombolytic treatment and those considered unsuitable for this treatment in this survey, as in previous studies,[5] probably reflects differences in patient baseline characteristics between the 2 groups in addition to the expected beneficial effect of thrombolysis. However, it is worth mentioning that the difference in mortality rates persisted after age-adjusted analysis, and that 60% of patients in the thrombolytic group had an anterior AMI, usually considered as a factor disposing to increased risk.

Despite rapid resolution of many controversial issues in coronary thrombolysis, much remains to be done in order to increase the number of patients with AMI who may be treated with thrombolytic agents.

**Acknowledgment:** We are indebted to all the nurses and physicians working in the coronary care units who participated in the survey.

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## APPENDIX

**Participating centers and investigators:** Assaf Harofe Hospital, Zrifin: Zwi Schlesinger; Barzilai Medical Center, Ashkelon: Leonardo Reisin; Beilinson Medical Center, Petach Tikva: Jacob Agmon, Yaacov Friedman, Samuel Sclarovsky; Bnei-Zion Hospital, Haifa: Edward Abinader; Carmel Hospital, Haifa: Abraham Palant; Central HaEmek Hospital, Afula: Tiberio Rosenfeld; Edith Wolfson Medical Center, Holon: Yehezkiel Kishon, Daniel Brunner; Hasharon Hospital, Petach Tikvah: Izhar Zahavi; Hillel Yaffe Hospital, Hadera: Benyamin Pelled; Ichilov Hospital, Sorasky Medical Center, Tel Aviv: Shlomo Laniado, Libi Sherf; Kaplan Hospital, Rehovot: Avi Caspi; Meir Hospital, Sapir Medical Center, Kfar Saba: Daniel David; Naharia Hospital, Naharia: Nathan Rougin; Rambam Medical Center, Haifa: Vladimier Markiewicz; Rivka Ziv Hospital, Tsfat: Michael Flich, Alon Marmor; Shaare Zedek Medical Center, Jerusalem: Monty Zion; Sheba Medical Center Heart Institute, Tel Hashomer: Elieser Kaplinsky, Babeth Rabinowitz; Soroka Medical Center, Beersheva: Moshe Gueron, Natalio Kristal.

# Effect of Propranolol (Long-Acting) on the Circadian Fluctuation of Tissue-Plasminogen Activator and Plasminogen Activator Inhibitor-1

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**The incidence of myocardial infarction and sudden cardiac death is highest in the morning. Inhibition of fibrinolytic activity in blood also peaks in the morning and this inhibition may favor the development of arterial thrombosis. It has been reported that patients treated with β blockers do not show the typical circadian pattern of onset of myocardial infarction and sudden cardiac death. This study was undertaken to investigate whether β blockade alters the circadian rhythm of 2 major fibrinolytic factors, tissue-plasminogen activator (t-PA) and plasminogen activator inhibitor-1 (PAI-1). Repeated blood samples were taken over a 24-hour period in 13 healthy volunteers: 7 taking 160 mg/day of long-acting propranolol orally for 14 days, and the other 6 taking no medications. Blood samples were analyzed for the plasma levels of t-PA activity, t-PA antigen, PAI activity and PAI-1 antigen. A significant circadian variation of all 4 parameters was present in both groups. No significant differences in peak and nadir values, 24-hour mean, amplitude of fluctuation, and time of peak and nadir were found between the treated and untreated subjects. The data therefore suggest that propranolol treatment does not affect the plasma concentrations at rest or the endogenous circadian rhythm of t-PA and PAI-1 in healthy volunteers. The reported alteration in the circadian pattern of onset of myocardial infarction and sudden cardiac death by β blockers does not appear to be mediated by effects on the fibrinolytic system.**

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Myocardial infarction and sudden cardiac death occur more frequently in the morning.[1,2] A possible explanation for this phenomenon is the circadian variation of potential pathogenetic factors, such as platelet aggregability,[3] blood anticoagulant activity,[4] circulating catecholamines,[5] blood pressure,[6] heart rate[6] and vasomotor tone.[7] It has been noted that treatment with β-receptor blockers modifies the circadian pattern of onset of myocardial infarction[8,9] and sudden cardiac death.[10] It is possible therefore that β blockade alters the circadian variation of underlying precipitating factors.

Two major determinants of the fibrinolytic balance in blood, tissue-plasminogen activator (t-PA) and its fast-acting inhibitor, plasminogen activator inhibitor-1 (PAI-1), show a marked circadian fluctuation both in normal subjects[11] and in patients with stable arterial disease.[12] Lowest fibrinolytic activity due to elevated PAI-1 levels is observed in the early morning in temporal concordance with the peak incidence of acute thrombotic events. Patients with unstable angina[13] or with evolving acute myocardial infarction[13,14] show a similar circadian pattern. Moreover, increased plasma activity of PAI-1 has been associated retrospectively with the occurrence of myocardial infarction[15] and prospectively with reinfarction.[16,17]

In the present study we have investigated the effects of a nonselective β-blocker agent on the circadian rhythm of plasma t-PA and PAI-1. The rationale of the study was the following: if an alteration in the circadian variation of these factors was observed during β blockade, a close relation between the circadian pattern of fibrinolytic factors and that of arterial thrombosis might be assumed. Conversely, in case of an unchanged circadian rhythm of t-PA and PAI-1 during β blockade, a primary role of the endogenous fibrinolytic system in determining the circadian pattern of onset of acute cardiovascular events would appear less likely.

## METHODS

**Subjects:** Two groups of healthy volunteers were investigated: a study group of 7 subjects (6 men, 1 woman; mean age 33.3 ± 1.4 years, range 29 to 40) taking propranolol, and a control group of 6 subjects (4 men, 2 women; mean age 29.2 ± 2.5 years, range 23 to 39)

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taking no medications. None were hypertensive, obese, hyperlipidemic, or had a history of thrombotic disorders, asthma, sleeping disturbances or recent illnesses. The women were not taking oral contraceptive drugs. One subject in the study group was a smoker.

**Beta-blocker administration:** The volunteers forming the study group received a slow-release preparation of the nonselective β-receptor blocker, propranolol hydrochloride (Inderal LA®, Imperial Chemical Industries PLC, Macclesfield, Cheshire, UK), administered in a single daily oral dose of 160 mg for 14 consecutive days. Compliance to treatment was monitored by 3 daily recordings of the pulse rate and blood pressure before and during the period of propranolol administration. Blood collection was begun on the morning of the last day of administration.

**Blood samples:** Serial blood samples were obtained from each subject every 3 hours over a 24-hour period, starting at 9:00 A.M. During this period, the volunteers pursued their normal activities during the day and slept in a hospital ward between midnight and 8:00 A.M. A peripheral venous cannula was inserted 15 minutes before the first sample; the cannula was kept patent by flushing it with 25 IU of heparin after the withdrawal of blood. In the hour preceding each blood sample the subjects refrained from strenuous exercise, eating, drinking and smoking. The first 2 ml of blood were discarded and the following 9 ml were collected in cooled plastic tubes containing 1 ml of 0.103 M trisodium citrate. After immediate centrifugation at 2,000 × g for 20 minutes at 4°C, the resulting platelet-poor plasma was aliquoted, snap-frozen and stored at −70°C.

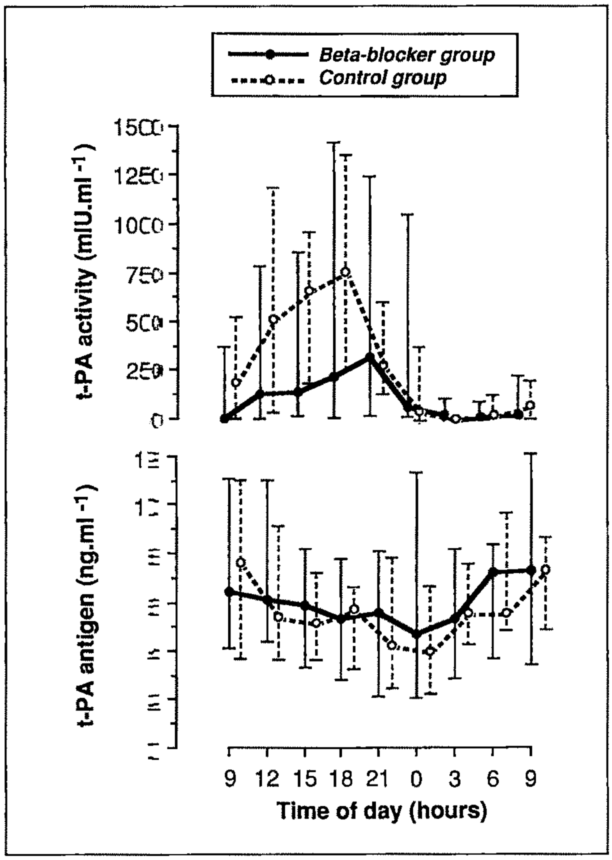

**FIGURE 1. Median plasma levels of tissue-plasminogen activator (t-PA) activity (*above*) and t-PA antigen (*below*) over a 24-hour period in the volunteers taking propranolol (*continuous curve*) and in those taking no medications (*broken curve*). *Bars* represent ranges.**

**Fibrinolytic factors:** The plasma aliquots corresponding to each blood collection time were analyzed for the activity and antigen levels of t-PA and PAI-1. t-PA activity was measured in plasma euglobulin fractions by a parabolic rate chromogenic assay.[18] Calibration was performed using the international t-PA standard.[19] Values are expressed in $mIU{\cdot}ml^{-1}$ of plasma. t-PA antigen concentrations were measured by a specific enzyme-linked immunosorbent assay using a slightly modified version of the Imulyse t-PA (v 1-5) kit (Biopool, Umea, Sweden; catalogue number 101005). Values are expressed in $ng{\cdot}ml^{-1}$. PAI activity was assessed by titration with known amounts of standard t-PA and measurement of residual t-PA activity as previously described.[20] Values are expressed in $IU{\cdot}ml^{-1}$. PAI-1 antigen concentrations were measured by a specific enzyme-linked immunosorbent assay using the TintElize PAI-1 kit (Biopool, Umea, Sweden; catalogue number 210220). Based on a previous validation of our blood-collection procedure,[21] we excluded any significant platelet contribution to the PAI-1 antigen levels. Values are expressed in $ng{\cdot}ml^{-1}$.

**Statistical analysis:** Results are expressed as mean ± standard deviation or as median with range. For normally distributed parameters, differences were analyzed using Student's *t* tests. Otherwise, the Wilcoxon signed rank test and the Mann-Whitney U test were applied. When identical values were recorded at consecutive sampling times, the median time was taken. The Bonferroni correction was applied to multiple comparisons. A p value $\leq 0.05$ was considered statistically significant.

## RESULTS

In the group taking propranolol, the pulse rate was 69.6 ± 4.6 beats/min before and 57.1 ± 9.0 beats/min at the end of treatment ($p = 0.002$). Systolic blood pressure was 119.3 ± 5.3 mm Hg before and 105.3 ± 5.7 mm Hg at the end of propranolol administration ($p = 0.001$). Diastolic blood pressure was 79.6 ± 4.6 mm Hg before and 66.4 ± 8.5 mm Hg at the end of treatment ($p = 0.01$). No serious side effects were reported by the subjects taking propranolol.

Figure 1 shows the median plasma levels of t-PA activity and t-PA antigen over the 24-hour period in the 2 groups of volunteers. A significant difference in the activity and antigen levels of t-PA was found between

**TABLE I** Main Characteristics of the Circadian Pattern of Fibrinolytic Factors in Subjects Taking Propranolol and in the Control Group of Volunteers*

| | t-PA Activity | | t-PA Antigen | | PAI Activity | | PAI-1 Antigen | |
|---|---|---|---|---|---|---|---|---|
| | βB | CTR | βB | CTR | βB | CTR | βB | CTR |
| 24-hour peak†‡ | 447<br>(16–1,414) | 758<br>(260–1,343) | 8.2<br>(5.0–11) | 7.5<br>(5.1–9.5) | 17<br>(9.0–30) | 14<br>(12–20) | 28<br>(9.0–47) | 19<br>(14–56) |
| 24-hour nadir†‡ | 2.4<br>(0–46) | 0.8<br>(0–13) | 4.7<br>(2.1–5.9) | 3.8<br>(2.2–6.5) | 2.9<br>(1.1–4.3) | 3.8<br>(2.3–5.4) | 1.6<br>(0–8.1) | 4.5<br>(2.3–7.0) |
| 24-hour average†‡ | 125<br>(6.8–568) | 294<br>(88–563) | 6.4<br>(3.4–8.2) | 5.3<br>(3.9–7.8) | 7.3<br>(4.6–13) | 6.9<br>(5.2–9.9) | 14<br>(3.0–20) | 11<br>(6.1–19) |
| Amplitude of circadian fluctuation†‡ | 446<br>(14–1,412) | 757<br>(260–1,330) | 3.7<br>(2.6–6.2) | 4.2<br>(2.4–5.5) | 13<br>(7.0–28) | 10<br>(8.4–15) | 24<br>(12–46) | 14<br>(10–49) |
| Time of peak†§ (hours) | 1800<br>(0300–2100) | 1800<br>(1500–1800) | 0900<br>(0000–1200) | 0900<br>(0600–0900) | 0300<br>(0000–0900) | 0300<br>(0300–0600) | 0300<br>(0000–0900) | 0300<br>(0300–0600) |
| Time of nadir†§ (hours) | 0300<br>(0000–0900) | 0345<br>(0130–0600) | 0000<br>(1500–0130) | 0000<br>(2100–0300) | 1800<br>(1200–1930) | 1800<br>(1630–1930) | 1800<br>(1500–2100) | 1800<br>(1500–2100) |

*None of the parameters differed significantly between the 2 groups.
†Median values (ranges in parenthesis).
‡Values expressed in the respective units: t-PA activity in mIU · ml$^{-1}$, t-PA antigen and PAI-1 antigen in ng · ml$^{-1}$, and PAI-1 activity in IU · ml$^{-1}$.
§Time expressed in hours and minutes.
βB = β-blocker group; CTR = control group; t-PA = tissue-plasminogen activator; PAI and PAI-1 = plasminogen activator inhibitor-1.

values at the time of peak and those at the time of nadir (p <0.01) in both groups of subjects.

Figure 2 illustrates the median plasma concentrations of PAI activity and PAI-1 antigen during the 24 hours in the treated and untreated volunteers. A significant difference in the activity and antigen levels of PAI-1 was found between values at the time of peak and those at the time of nadir (p <0.01) in both groups of subjects.

The following parameters were assessed for each fibrinolytic factor: peak and nadir value during the 24-hour period, 24-hour averaged value, amplitude of the circadian fluctuation, time of occurrence of peak and nadir. No significant difference in any of these parameters was found between the propranolol-treated and the untreated group of subjects. The findings are summarized in Table I.

## DISCUSSION

This study demonstrates that the circadian fluctuation of the fibrinolytic factors, t-PA and PAI-1, is not significantly altered by β-adrenergic blockade. The plasma levels of these factors also do not appear to be significantly affected by propranolol treatment. We believe this is the first report of the effects of β blockade on specific components of the fibrinolytic system monitored over a 24-hour period. Our data further suggest that none of the multiple consequences of β blockade — including bradycardia, reduced blood pressure and cardiac output, increased peripheral resistance, or inhibition of lipolysis and glycogenolysis — influence the plasma levels or the circadian rhythm of t-PA and PAI-1.

We chose the nonselective β-receptor blocker propranolol because it was the most widely used β blocker agent at the time the altered circadian pattern of onset of myocardial infarction in treated patients was reported.[8] It was also the drug under investigation in the report on sudden cardiac death.[10] The propranolol regimen of 160 mg/day of a slow-release preparation achieved adequate β blockade in our subjects, as apparent from the significant reduction in pulse rate and blood pressure observed at the end of the 14-day treat-

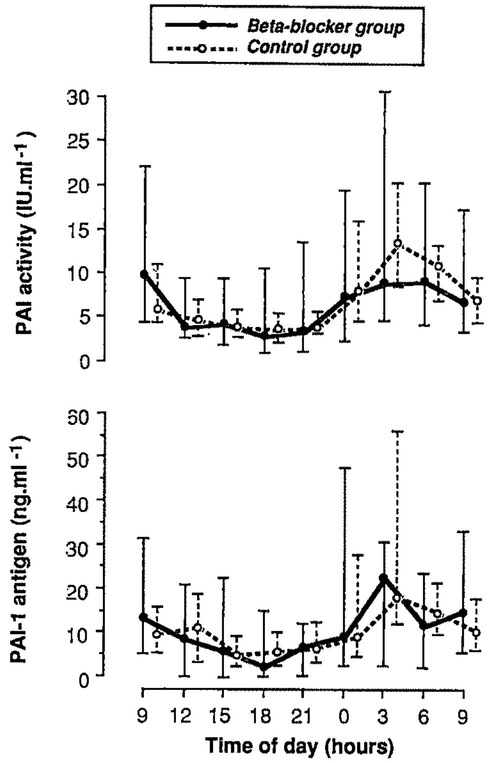

**FIGURE 2. Median plasma concentrations of plasminogen activator inhibitor-1 (PAI or PAI-1) activity (*above*) and PAI-1 antigen (*below*) over a 24-hour period in the subjects taking propranolol (*continuous curve*) and in those taking no medications (*broken curve*). *Bars* represent ranges.**

ment. The administration of propranolol for 14 days was considered necessary, as any interference by $\beta$ blockers with the endogenous pacemaker controlling the circadian rhythm of t-PA and PAI-1, if present, would probably have required several 24-hour periods before reaching a stable effect.

The consistency of the data between the propranolol-treated and the untreated group of subjects is striking. Because this was not a crossover study, i.e., different subjects formed the 2 groups, there are 2 possible interpretations of the results: either $\beta$ blockade had no effect on the investigated parameters, or some baseline differences between the 2 groups were exactly counterbalanced by the $\beta$-blocker treatment. The first interpretation appears by far the more likely. The somewhat lower t-PA activity levels observed in the $\beta$-blocker group (Figure 1, upper panel, and Table I) did not represent a statistically significant difference and are compatible with the slightly older age and the presence of a smoker in this group, since both age and chronic cigarette smoking are known to reduce blood fibrinolytic activity.[22,23] However, because of the small sample size, we cannot entirely exclude that the lower daytime t-PA activity in the $\beta$-blocker group represents a true phenomenon. In this case, the altered circadian rhythm of onset of myocardial infarction by $\beta$ blockers could be explained by a greater incidence of infarction during the day, when t-PA activity is depressed. This explanation, however, is in disagreement with the reported reduction of reinfarction rate in patients treated with $\beta$ blockers.[24]

Theoretically, $\beta$ blockade could have shifted the plasma concentrations of both t-PA and PAI-1 in the same direction, leaving the net fibrinolytic activity of plasma unchanged. To assess this possibility, in addition to the activity of t-PA and PAI-1, the immunoreactive forms, or antigen concentrations, were measured and found to be virtually unaffected by $\beta$-blocker treatment (Figures 1 and 2, lower panels).

We are aware of only 1 study investigating the effect of acute $\beta$ blockade on the diurnal changes of blood fibrinolytic activity.[25] In that study global fibrinolytic activity, assessed as plasma euglobulin lysis time, was measured over an interval of 2 hours; the intravenous administration of propranolol, alone or in combination with the $\alpha$-blocker phentolamine, did not have any effect on fibrinolytic activity, in agreement with our findings.

The lack of effect of $\beta$ blockade on the circadian rhythm of circulating fibrinolytic factors is not entirely surprising. Although it is known that intravenous adrenaline administration is followed by a prompt increase in blood fibrinolytic activity[26] and that pretreatment with propranolol can significantly inhibit the fibrinolytic response to adrenaline infusion,[27,28] the enhancement of fibrinolysis induced by the diurnal rhythm[29] or by exercise[29] does not appear to be mediated by circulating catecholamines and adrenoreceptor stimulation.[25,30] Still, $\beta$ blockade might exert an inhibitory effect on fibrinolytic activity, which is detectable only in the presence of enhanced adrenergic stimulation. In this respect, the resting condition of our healthy volunteers probably differs considerably from the condition of acutely ill patients with coronary thrombosis in whom adrenergic activation is likely to be high. We cannot exclude that the intensity of adrenaline-induced fibrinolysis itself undergoes a circadian variation that is blunted by $\beta$ blockade. It is also possible, but not very likely, that in patients with arterial disease the response of circulating fibrinolytic factors to $\beta$ blockers differs from that of young healthy subjects.

In conclusion, if $\beta$ blockade indeed alters the circadian pattern of onset of myocardial infarction and sudden cardiac death, our results suggest that the phenomenon is independent of fibrinolysis. The effects of $\beta$-receptor stimulation, including increased heart rate and cardiac output, which undergo changes over the 24 hours and are enhanced by the early morning adrenergic surge, may play a more crucial role in determining the higher morning frequency of acute coronary events. The contribution of the endogenous fibrinolytic system to the circadian pattern of onset of these events would appear to be, at most, subsidiary. The results of this study, however, do not undermine the possible importance of circulating fibrinolytic factors in promoting or regulating the development of acute thrombotic syndromes.

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# Specificity and Sensitivity of QRS Criteria for Diagnosis of Single and Multiple Myocardial Infarcts

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and Galen S. Wagner, MD

**A subset of 3 criteria from the complete Selvester scoring system has been proposed earlier for electrocardiographic screening of healed myocardial infarcts. This subset yielded 95% specificity and high sensitivity for single anterior and inferior infarcts. In the present study, an automated version of these criteria was applied to 1,344 electrocardiograms from normal subjects (473 normal subjects as determined by cardiac catheterization and 871 apparently normal subjects by history and physical examination), to 706 from subjects with single myocardial infarction, and to 131 from subjects with combined anterior and inferior myocardial infarcts. Of the single infarcts, 366 had inferior, 277 anterior and 63 posterolateral locations. Presence and location of infarcts were judged from left ventriculograms and coronary angiograms. Overall specificity was only 86%, whereas overall sensitivity for the infarct population was 77%. Specificity was lower in men than in women; it was also lower in older than in younger subjects. One of the screening criteria (R ≥40 ms in $V_1$) may possibly be eliminated to augment specificity; this can be done with only minor loss of sensitivity. Differences in wave form measurements between the manual and computer methods account for a large part of the deterioration of specificity in this study compared with previously published results. Computer application of the screening criteria requires altered criteria limits in comparison with those used in manual application. Probably sex- and age-dependent criteria limits should be used.**

**(Am J Cardiol 1991;68:1300–1304)**

Acute myocardial infarction is diagnosed by the combination of serial changes in the electrocardiograms and enzymes. The electrocardiogram is the single readily available method for diagnosis of healed infarction. Previous studies[1,2] demonstrated superiority of vectorcardiographic over classic electrocardiographic (ECG) criteria for this diagnosis, and automated analysis systems employ very complex criteria in an attempt to compensate. The study of Anderson et al[3] identified 3 criteria from the complete Selvester scoring system[4] to "screen" for presence of myocardial infarcts that achieved high specificity (95%), and sensitivity similar to that of the vectorcardiographic criteria. Each criterion relates to one of the common infarct locations (inferior, anterior, and posterolateral) that result from occlusions of the 3 major coronary arteries (the right, left anterior descending and left circumflex, respectively). These screening criteria have not yet been evaluated in a test population, perhaps because of the inconsistent and tedious process required for manual application of quantitative criteria. Recently, however, Pope et al[5] developed an automated method of applying the Selvester scoring system, which removes these problems from such an evaluation. The main purposes of this study were to test the specificity of the screening criteria in normal subjects and their sensitivity in patients with single or multiple infarcts using the automated method.[5] Secondary purposes were to study the influence of varying criteria limits and of deleting criteria on sensitivity/specificity.

## METHODS

**Study population:** The normal study group consisted of 1,344 subjects. Of these, 473 had undergone diagnostic cardiac catheterization at the North Carolina Baptist Hospital during the period 1981 to 1986. Criteria for this subgroup were similar to those of the study by Hindman et al[4]: no ECG evidence of right or left ventricular hypertrophy, bundle branch block or fascicular block as determined by the Marquette 12-SL program (Marquette Electronics, Inc., Milwaukee, Wisconsin), normal coronary arteries, normal contrast left ventriculogram, no evidence of valve dysfunction or congenital heart disease, ejection fraction ≥50%, and

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an overall study evaluation of "normal." The remaining 871 persons were from the Marquette Normal Data Base. These were normal volunteers or subjects undergoing routine health screening examinations. History and physical examination revealed that they were free of any disease known to affect the electrocardiogram, took no medications other than aspirin, were normotensive, and had been examined by a cardiologist to exclude organic murmurs or mitral valve prolapse. Subjects with known prior elevation of cholesterol, family history of diabetes or heart disease diagnosed before age 50 years were excluded. The same ECG exclusion criteria as for the catheterization normal group were applied. The demographic characteristics of these study populations are listed in Table I.

The Wake Forest University Catheterization Registry was searched to identify patients with healed single inferior, anterior, or posterolateral myocardial infarction, or combined anterior and inferior infarctions (Table I) with the same ECG and noncoronary exclusions as for the catheterization normal study group. The criteria for single anterior and inferior myocardial infarcts described next were similar to those of Anderson et al.[3]

Three hundred sixty-six patients had single inferior myocardial infarcts defined as indicated in Table II and Figure 1 by presence of ≥75% diameter stenosis of the right coronary artery, and akinesia or dyskinesia of the inferior wall on the right anterior oblique ventriculogram (segments 1 or 2). Two hundred seventy-seven patients had single anterior myocardial infarcts defined by presence of ≥75% diameter stenosis of the left main coronary artery, the left anterior descending artery or its major diagonals, and akinesia or dyskinesia of the anterior-superior wall on the right anterior oblique ventriculogram (segments 3, 4 or 5). Sixty-three patients had single posterolateral myocardial infarcts defined by presence of ≥75% diameter stenosis of the left circumflex artery or any of its major branches in conjunction with akinesia or dyskinesia of the posterolateral wall on the left anterior oblique ventriculogram (segment 7).

One-hundred thirty-one patients had both anterior and inferior myocardial infarcts defined by ≥75% diameter stenosis of the left main artery, the left anterior descending artery or its major diagonals, and also of the right coronary artery accompanied by akinesia or dyskinesia of the anterior and inferior walls of the right anterior oblique ventriculogram (Table II).

**TABLE I** Demographic Characteristics of Study Population

| | Normal | | Infarction | | | |
|---|---|---|---|---|---|---|
| | Catheterized | Volunteers | I | A | PL | A + I |
| No. of pts. | 473 | 871 | 366 | 277 | 63 | 131 |
| Men (%) | 39 | 68 | 80 | 81 | 83 | 76 |
| Women (%) | 61 | 32 | 20 | 19 | 18 | 24 |
| Mean age (yr) | 51 | 44 | 56 | 55 | 56 | 59 |

A = anterior; I = inferior; PL = posterolateral.

**Electrocardiographic evaluation and data analysis:** Standard 12-lead electrocardiograms were recorded on computerized electrocardiographs (Marquette Electronics, Inc., Milwaukee, Wisconsin) near to the time of diagnostic cardiac catheterization or physical examination. Waveform measurements were performed by the software described in the study by Pope et al.[5] This software reanalyzes the QRS complex of the Marquette median beat and shortens Q-wave duration if a Q notch is found. The screening criteria are[3]: (1) Q ≥30 ms in aVF, (2) any Q or R ≤10 ms and R ≤0.1 mV in $V_2$, and (3) R ≥40 ms in $V_1$.

These relate to inferior, anterior and posterolateral locations, respectively. In criterion 2, the "any Q" aspect is stated directly, whereas in the original study by Anderson et al[3] it was simply assumed, because a Q wave would represent the extreme of a diminished R wave.

A subset of 200 electrocardiograms was selected for manual application of the screening criteria. Of these, 100 were from the normal group undergoing catheterization and 100 from the various infarct groups; half of each 100 had screened positive and half negative by the computerized method, presetting results at 50% specificity and 50% sensitivity. The manual observer was presented with median beats recorded at double speed and double gain, and was unaware of both clinical diagnosis and results of computer screening. Plots of the measurement distributions were generated to study the

**TABLE II** Criteria on Wall Motion and Coronary Status for Inclusion into Study Groups

| | Left Ventriculogram (segment no.) | | | | | | | Coronary Angiography | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Population | 1 | 2 | 3 | 4 | 5 | 6 | 7 | Right | LM/LAD | LC |
| Catheterized normal | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Inferior MI | (+ or +) | | 0 | 0 | 0 | +/0 | +/0 | + | +/0 | +/0 |
| Anterior MI | 0 | 0 | (+ or + or +) | | | +/0 | 0 | +/0 | + | +/0 |
| Posterolateral MI | 0 | +/0 | 0 | 0 | 0 | 0 | + | +/0 | +/0 | + |
| Anterior + inferior MI | (+ or +) | | (+ or + or +) | | | +/0 | +/0 | + | + | +/0 |

Wall segment numbers refer to Figure 1.
LC = left circumflex coronary artery; LM/LAD = left main or left anterior descending artery or its major diagonals; MI = myocardial infarction; + = akinesia or dyskinesia/ ≥75% stenosis; 0 = normal motion/no stenosis; +/0 = may be normal or abnormal; (+ or +) = either segment or both abnormal; (+ or + or +) = ≥1 of 3 segments abnormal.

**TABLE III** False-Positive Rates (%) for Screening Criteria

| Criterion Fulfilled | False-Positive Rate |
|---|---|
| aVF alone | 4.1 |
| aVF alone or in combination | 5.5 |
| $V_2$ alone | 4.6 |
| $V_2$ alone or in combination | 5.1 |
| $V_1$ alone | 3.7 |
| $V_1$ alone or in combination | 4.9 |
| Screening set | 14 |

Criteria: aVF: Q >30 ms; $V_2$: any Q or R <0.1mV; $V_1$ R >40 ms.

**TABLE IV** Specificities (%) for Set of Screening Criteria in Various Age Groups

| Age Group (yr) | No. of Pts. |  | Specificity |  |  |
|---|---|---|---|---|---|
|  | Women | Men | Women | Men | p Value |
| –39 | 130 | 254 | 92 | 84 | 0.0169 |
| 40–49 | 138 | 246 | 94 | 85 | 0.0105 |
| 50–59 | 157 | 182 | 88 | 87 | 0.765 (NS) |
| 60– | 144 | 93 | 84 | 76 | 0.141 (NS) |
| Total | 569 | 775 | 89 | 84 | 0.0055 |

effect that varying the criteria thresholds had on sensitivity and specificity. The chi-square test was used to assess the significance of the difference in sensitivity or specificity of the criteria set between different study groups.

## RESULTS

Because the $V_2$ criterion consists of multiple components (any Q or R ≤10 ms and ≤0.1 mV), the performance of each of these was initially evaluated. One hundred seventy of 277 patients (61%) met the any Q criterion, but only 6 others (2.2%) met both of the R criteria. An additional 35 patients (13%) met only the R-amplitude component, but none met the R-duration component alone. Because this result contrasted with that reported using manual measurement by Anderson et al,[3] R-duration measurements by automated versus manual methods were compared. In 16 of the 200 patients evaluated, the R-duration component was satisfied by manual interpretation. Automated measurement concurred in only 6 cases; the computer-measured duration ranged from 0 ms (i.e., no R wave found) to 20 ms (median 12). Therefore, it was decided to perform all subsequent analysis with a simplified version of the $V_2$ screening criterion (any Q or R ≤0.1 mV).

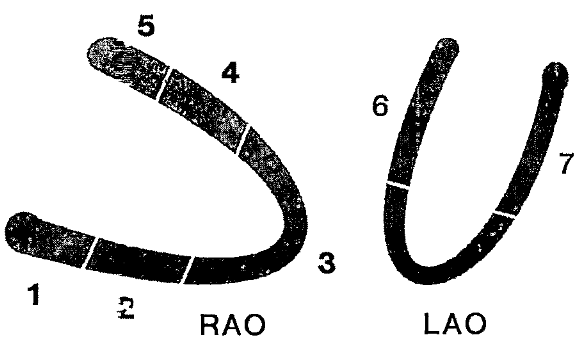

**FIGURE 1.** ***Left panel,*** **wall segments of right anterior oblique (RAO) ventriculogram;** ***right panel,*** **wall segments of left anterior oblique (LAO) ventriculogram.**

**TABLE V** Sensitivities (%) of Screening Criteria in Various Myocardial Infarction Populations

|  | Sensitivity |  |  |  |
|---|---|---|---|---|
| Criterion Fulfilled | I | A | PL | A + I |
| aVF alone | 59 | 2.2 | 33 | 31 |
| aVF alone or in combination | 71 | 12 | 48 | 54 |
| $V_2$ alone | 3.0 | 67 | 3.2 | 23 |
| $V_2$ alone or in combination | 6.3 | 76 | 3.2 | 42 |
| $V_1$ alone | 2.7 | 0.4 | 11 | 0.8 |
| $V_1$ alone or in combination | 11 | 1.1 | 25 | 6.2 |
| Screening set | 77 | 79.4 | 62 | 78 |

Criteria: aVF: Q >30 ms; $V_2$: any Q or R <0.1 mV; $V_1$: R >40 ms.
A = anterior; I = inferior; PL = posterolateral.

The overall specificity of the set of 3 screening criteria was 86%. The false-positive rates for the individual criteria are presented in Table III. Although 185 persons (14%) met at least 1 of the 3 criteria, only 18 (1.3%) met >1 criterion. The overall performance of the screening criteria in the various age and sex groups is shown in Table IV. There was a trend toward decreasing specificity with age within both female and male populations. This difference was significant between women in 40s versus 50s and for both sexes in 50s versus 60s. Specificity was lower in men than in women in all age groups, but the differences attained statistical significance only in the 2 younger age groups.

The overall sensitivity of the screening set was 77%. The sensitivities were essentially the same for the single (77%) and multiple (78%) infarct groups. The sensitivities of the screening criteria in the various infarct populations are listed in Table V. Sensitivities of 79 and 77% in the single anterior and inferior infarct groups were similar (p = 0.57; difference not significant), but were significantly higher than the 62% of the posterolateral infarct group (p = 0.0032 and p = 0.012, respectively). In the inferior infarct group, the aVF criterion was highly sensitive (71%). Within the anterior infarct group the $V_2$ criterion achieved a high sensitivity (76%), but there was also a 12% incidence of the aVF criterion. In the posterolateral group, none of the 3 criteria achieved high sensitivity, with the 48% by the aVF criterion being greatest. There was only 25% sensitivity for the $V_1$ criterion. The aVF and $V_2$ criteria both achieved lower sensitivity in patients with combined anterior and inferior infarcts than in those with single inferior or anterior infarcts, respectively. However, they contributed similarly (54 and 42%) to the diagnosis of the multiple infarcts and complemented each other to achieve the overall high sensitivity of 78%.

The specificity of the screening set (86%) is lower in this study than in that by Anderson et al[3] (95%; p = 0.001). Because automated technology facilitates more precise waveform duration measurements, the effect of incrementally varying the criteria was determined. Figure 2 indicates an example of the effects on sensitivity/specificity of varying the threshold of Q-wave duration in aVF in the vicinity of the value used in this study. Maintenance of the 30 ms threshold would preclude addition of any other screening criterion without excessive loss of specificity. The threshold of 34 ms required to permit inclusion of even 1 more screening criterion would result in a decrease in sensitivity from 71 to 58%.

The $V_1$ criterion alone has a false-positive rate (4.9%) similar to that of the aVF criterion (4.1%). Since it has a much lower sensitivity, perhaps elimination rather than modification might be most appropriate. The specificity of the resulting set of 2 criteria would increase by 3.7 to 90%, whereas the sensitivity for the total infarction population would decrease by 2.3 to 74%.

The result of manual versus computer screening of the 200 patient subset was considered to determine the extent to which the differences in performance could be explained by the difference in methods. Computer screening concurred with visual screening in 175 cases (88%). In the 25 cases of disagreement, the correct diagnosis was achieved by the human observer in 20 cases and by the computer in 5 cases. Overt computer mismeasurements were observed particularly in lead aVF (Figure 3).

## DISCUSSION

It is a matter of judgment to determine the optimal limits of normal for any test, with the relative trade-offs in sensitivity and specificity considered. Since the standard 12-lead electrocardiogram is used so widely as a screening method, it is of prime importance that high specificity be attained. Most clinicians would agree that false-positive identification of an important clinical entity such as a healed myocardial infarction should not exceed 5%. Such results were achieved for the screening set by Anderson et al.[3] It is not surprising that this low level was not corroborated by the present study because in the original study (1) no test group was involved, (2) there was no blinding of the patient diagnosis, and (3) manual QRS measurements were performed. Indeed, the high sensitivity attained by Anderson et al[3] suggested that it would be unlikely that their combination of high sensitivity and specificity would be confirmed in an independent test group.

However, it is surprising that there were 14% false-positive results identified in the present study. The criteria for "normal" for catheterized patients are very strict and are essentially identical in the 2 studies.

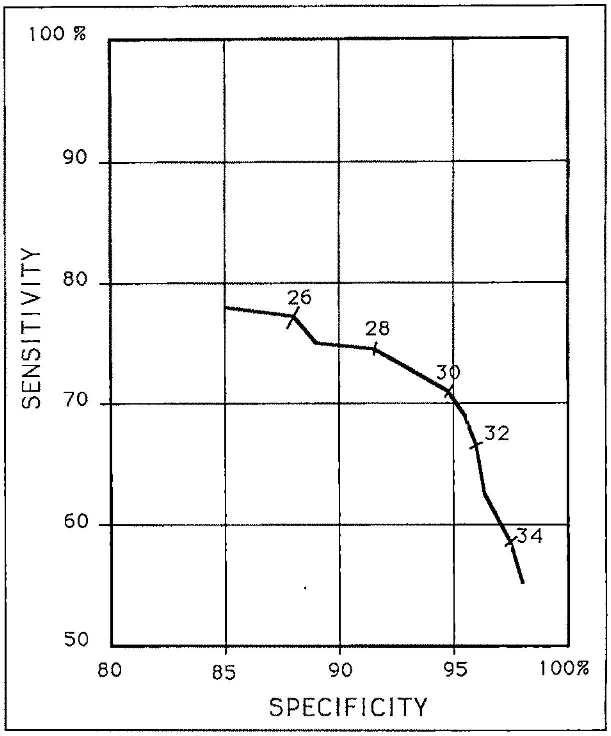

**FIGURE 2. Sensitivity versus specificity of the aVF criterion for thresholds ranging from 25 to 35 ms. Sensitivity was determined for the 366 patients with angiographically diagnosed inferior myocardial infarction. Specificity was determined for the total group of 1,344 normal subjects.**

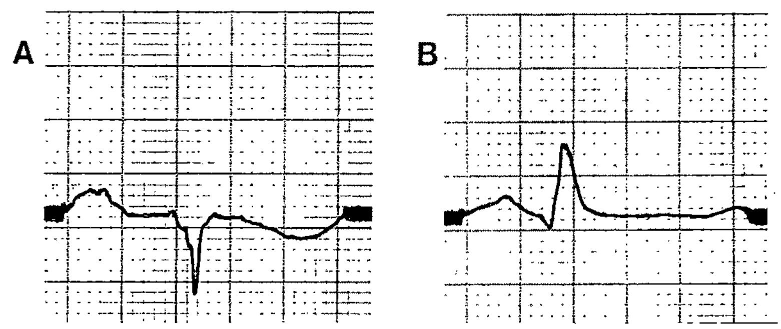

**FIGURE 3. Two examples indicating computer mismeasurements in lead aVF. *A*, small initial R wave is missed, so the computer measures a wide Q wave; *B*, QRS is erroneously delineated at the peak of the P wave. Q-wave duration is therefore grossly overestimated.**

Therefore, it is unlikely that a significant number of the current normal subjects who had undergone catheterization had unrecognized myocardial infarction. The validity of the results of the present study is enhanced by finding similar specificity in the volunteer group.

The primary reason for the difference in specificities is most likely the differing methods, manual versus automated. As indicated in the comparison of measurement methods in the 200 electrocardiograms in the text and illustrated in Figure 3, computer measurement was at times responsible for false application of screening criteria. For example, small R waves preceding large S waves were not recognized and the depressed waveform during the PR segment was considered a Q wave. Possibly some of these errors could be corrected in a manual-reviewing phase much in the same way as computer interpretations are most often reviewed by an experienced electrocardiographer. Ultimately, however, efforts must be made to improve computer waveform measurements.

The present study confirms the high sensitivities of Anderson et al[3] with single anterior and inferior infarcts. As expected, both the aVF criterion for inferior infarction and the $V_2$ criterion for anterior infarction individually achieved lower sensitivities in patients with combined anterior and inferior infarction. However, when both of these criteria are applied, the sensitivity for combined infarction is equal to but not greater than that for single infarction.

There proved to be systematic differences between the manual method and the computer method with regard to the duration component of the $V_2$ criterion. It was therefore disregarded, leaving a simplified version of the $V_2$ criterion. In the aVF criterion, the Q-wave duration is defined as the duration from QRS onset to either the peak of any notch within the Q wave or (if no notch is present) to the end of Q. This definition is different from the one used in commercially available ECG measurement and interpretation programs, and is used because only the initial part of the QRS is typically deformed by an inferior myocardial infarction.[4] It would be of interest to evaluate the influence of different definitions of Q-wave duration on sensitivity/specificity, but that was not within the scope of the present study.

There was no group with posterolateral infarction in the study of Anderson et al.[3] The $V_1$ criterion that added minimal sensitivity in patients with inferior and anterior infarction in that study might be expected to be highly sensitive in a posterolateral infarct group. However, only 7 of the 63 patients (11%) were identified solely by this criterion. This result is similar to that of 4 of 20 patients (20%) with anatomic posterolateral infarction reported by Ward et al.[6] The aVF criterion alone identified 3 times as many of the patients (33%) as did the $V_1$ criterion in the present study, which appeared alone only in 1 of the 131 patients with multiple infarcts. Overall sensitivity in the posterolateral infarct group would decrease from 62 to 51% if the $V_1$ criterion was eliminated.

This study suggests that a set of 2 screening criteria might achieve a specificity of 95% and high sensitivity for both single and multiple infarcts. Criteria limits may have to be sex- and age-dependent and be adjusted to within 1 ms for the aVF criterion and with 10 $\mu$V for the $V_2$ criterion.

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# Intracoronary Ultrasound Evaluation of Interventional Technologies

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**The feasibility and applicability of intravascular ultrasound (IVUS) of the coronary arteries were evaluated in 65 patients undergoing 70 coronary interventional procedures. Morphologic and quantitative analyses were performed with a mechanically rotated IVUS catheter (4.8Fr, 20 MHz) and with orthogonal view cineangiography. A semiautomated edge-detection algorithm was used for cineangiographic quantification. Coronary interventions included 45 percutaneous transluminal coronary angioplasties, 9 excimer lasers, 11 directional coronary atherectomies, 3 rotational atherectomies and 2 stents. Most lesions consisted of a mixture of plaque composition (hard, n = 30; soft, n = 64). Other unique morphologic data by IVUS were plaque topography (eccentric, n = 34; concentric, n = 36) and vessel dissection (IVUS [n = 29] versus angiography [n = 14], $p < 0.05$). Postprocedure minimal lumen diameter and cross-sectional area measured by IVUS were larger and poorly correlated with angiography (r = 0.28, standard error of the estimate = 0.52 mm; r = 0.08, standard error of the estimate = 1.0 $cm^2$, respectively). IVUS is more sensitive than angiography when assessing postintervention lesion characteristics including vessel dissection and plaque morphology. Catheter-based ultrasound appears to be a useful adjunct to contrast angiography when evaluating and comparing the therapeutic impact of conventional percutaneous transluminal coronary angioplasty with new technologies.**

**(Am J Cardiol 1991;68:1305–1309)**

Conventional contrast cineangiography provides a limited definition of vessel morphology at least partially due to silhouette imaging. However, cineangiography has been considered to be the gold standard for human in vivo assessment of luminal dimensions and extent of plaque disruption after coronary interventions. Previous studies have demonstrated the feasibility of catheter-based intravascular ultrasound (IVUS) to obtain quantitative and qualitative information of arterial anatomy in vivo and in vitro.[1–7] Real-time 2-dimensional ultrasound images have detected plaque composition,[2] postangioplasty dissection,[1,2] and thrombus.[6] In vitro imaging of postangioplasty segments has demonstrated plaque morphology and qualitative characteristics of plaque disruption.[1] Human in vivo data have demonstrated an excellent correlation between IVUS and quantitative angiography for assessment of peripheral arterial dimensions in normal and minimally diseased segments.[2] The purpose of this study was to determine the feasibility and applicability of IVUS to assess the acute effects of coronary interventional technologies.

## METHODS

**Patient group:** Seventy coronary interventions were prospectively evaluated in 65 patients. There were 48 men and 17 women (mean age 63 ± 6 years, range 49 to 76). The indication for intervention was progressive or unstable angina in all except 1 patient who presented with an acute myocardial infarction. Preprocedure angiographic stenosis was ≥75% by visual estimate in all patients. Eleven patients had undergone previous balloon coronary angioplasty.

Interventions performed were: 45 balloon percutaneous transluminal coronary angioplasties (PTCAs), 11 directional coronary atherectomies, 9 excimer lasers (4 of which were performed with adjunctive PTCA), 3 rotational atherectomies and 2 stainless steel stent implantations.

Coronary interventions were performed in a standard manner over a 0.014-inch guidewire through a 9Fr giant lumen-guiding catheter or a 9.5Fr or 11Fr guide catheter for patients undergoing atherectomy. The size of the interventional device was selected based

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on visual estimate of the angiographically normal vessel diameter using the guide catheter for calibration.

The sites of the 70 lesions were 29 right coronary arteries, 31 left anterior descending coronary arteries, 8 left circumflex coronary arteries and 2 saphenous vein grafts. All lesions were within the proximal or midsection of the vessel.

**Ultrasound imaging:** The coronary catheter used was a 4.8Fr monorail over-the-wire catheter (Boston Scientific Corporation, Watertown, Massachusetts). The catheter was advanced over a 0.014-inch guidewire immediately after the coronary intervention. A 20 MHz single piezoelectric crystal transducer is mechanically rotated within the catheter sheath and attached to a diagnostic imaging console (Diasonics, Inc., Milpitus, California). Two-dimensional images were displayed on a video monitor of 512 × 512 pixel matrix that discriminated 64 shades of gray. Images were recorded on 0.5-inch videotape for subsequent quantitative and qualitative analysis. Quantitative analyses was performed off-line with resident software from a Hewlett-Packard SONOS 1000 system (Andover, Massachusetts). If a dissection was present, the area within the true lumen and behind the flap was planimetered. Passage of the catheter-based ultrasound was successful in all patients in which it was attempted. There were no complications attributable to IVUS imaging.

In patients 1 to 6, the software configuration of the ultrasound system was not calibrated for quantitative determination. Postprocedure computer-derived quantitative measurements were obtained in 23 consecutive arterial segments for the image displaying minimal absolute lumen diameter and cross-sectional area. Due to the vast discordance of the 2 techniques, no further angiographic quantitation was obtained. Cross-sectional area was obtained by planimetry. Excellent intraobserver and interobserver correlations have been previously reported.[2]

Qualitative analyses were evaluated by 2 observers unaware of the results of angiography. Vessel morphology analyses were undertaken for plaque composition (hard versus soft), plaque topography (eccentric versus concentric) and vessel dissection.

Plaque composition was evaluated in a similar manner to that previously suggested by Gussenhoven et al.[3] Hard plaque was defined as vessel wall thickening with bright reflected echoes or distal acoustic shadowing consistent with calcium, or both. Soft plaque lacked these characteristics and was represented as less dense echoes of thickened arterial wall. Eccentric plaque was defined as involving <50% of the total circumference of the vessel. Dissection was defined as separation of plaque from intima or media with encroachment of plaque onto the catheter blank or with independent motion from the vessel wall. Equivocal dissections were confirmed by hand injection of contrast media through the guide catheter during ultrasound imaging. If a dissection was present, contrast was visualized within the true lumen and in the dissection plane.

**Contrast angiography:** Contrast cineangiography in orthogonal views was obtained before and after the intervention with hand injection of nonionic contrast. Images were acquired in a 7-inch image intensifier mode at 30 frames/s.

Quantitative digital cineangiographic images were analyzed with a previously validated, semiautomated edge-detection algorithm[8] in the same patients measured with ultrasound. The guide catheter was used for calibration. Absolute lumen diameter and cross-sectional area were determined at the same position as the coronary angiogram image displaying minimal lesion diameter and area.

Qualitative analysis of cineangiographic images were undertaken by consensus of 2 observers unaware of the angiography for determination of vessel dissection. Dissection was defined as either a linear filling defect within the vessel or an extraluminal opacity.[9]

**Data analysis:** The correlation between angiographic and intravascular ultrasound images was determined with linear regression. Categoric data were analyzed with a Breslow chi-square.

## RESULTS

**Quantitative data:** The absolute lumen diameter and cross-sectional area for 23 consecutive postinterventional arterial segments determined by angiography and ultrasound were poorly correlated ($r = 0.28$, standard error of the estimate = 0.52 mm, $p = 0.2$, and $r = 0.1$, standard error of the estimate = 1.0 cm$^2$, $p = 0.7$; respectively) (Figure 1). In general, IVUS measurements of vessel size were larger than with angiographic determinations.

**Qualitative data:** Although variability in image quality existed, IVUS provided morphologic information in all cases. Most lesions consisted of a mixture of both hard and soft plaque. Plaque composition was classified as hard in 30 (43%) lesions and soft in 64 (91%) lesions.

Evaluation of plaque topography revealed that eccentric lesions, comprising <50% of the vessel lumen, were observed in 34 lesions (49%), and concentric plaque was present in 36 lesions (51%).

In the 70 interventions qualitatively evaluated by IVUS and angiography, vessel dissection was noted by ultrasound in 29 segments (41%), and in only 14 segments (20%) by angiography ($x_b^2 = 9.8$; $p < 0.05$) There was concordance between the 2 techniques in 67% of sites. However, coronary dissections were noted by ultrasound at 19 sites (27%), in which they were not detected with angiography. Figure 2 demonstrates an example of a right coronary artery PTCA in which haziness but no obvious dissection is present at the dilation site. A large mobile intimal and medial dissection is present by ultrasound. Despite the ultrasound appearance, this patient had no acute adverse clinical events, and remains asymptomatic 7 months after-PTCA.

Angiography identified 4 dissections that were not detected by ultrasound. These occurred in vessels whose postintervention lesion diameters by angiography were <2.5 mm. The luminal flap noted by angiography was probably "tacked up" by the near-occlusive ultrasound catheter. In the 8 patients undergoing excimer laser angioplasty, hard plaque comprising >50% of the lesion was noted in 4 patients and predominantly soft plaque was observed in 4 patients. An example of soft plaque ablation is shown in Figure 3.

Vessel dissection was noted in 2 of 11 patients (18%) undergoing directional atherectomy and in 26 of 45 patients (58%) undergoing conventional balloon PTCA ($p < 0.05$). With catheter-based ultrasound, the extent of residual atheromatous plaque after atherectomy was well defined. In 10 of 11 atherectomy cases residual atheroma could be demonstrated with ultrasound despite an adequate angiographic result. Thus, the smooth vessel contour noted with silhouette contrast angiography appears to underestimate the extent of residual atheroma (Figure 4).

In the evaluation of intracoronary stainless steel stent deployment, conventional angiography is limited in its ability to visualize relatively radiolucent struts. IVUS readily defined the strut and vessel architecture (Figure 5). Although this patient incurred a major dissection after conventional PTCA, catheter-based ultrasound demonstrated resolution of dissection without persistent flap or luminal compromise.

## DISCUSSION

This study describes a series of patients in which IVUS was used to assess the acute effects of interventional technologies. Intracoronary ultrasound appears feasible and safe for postinterventional imaging. The advantage of this technique over contrast angiography is in its ability to define postinterventional lesion characteristics including lesion composition, topography and dissection.

It has been previously shown in postmortem studies that plaque morphology including topography and lesion composition are determinants of pathologic outcome after coronary angioplasty.[10] With IVUS, plaque

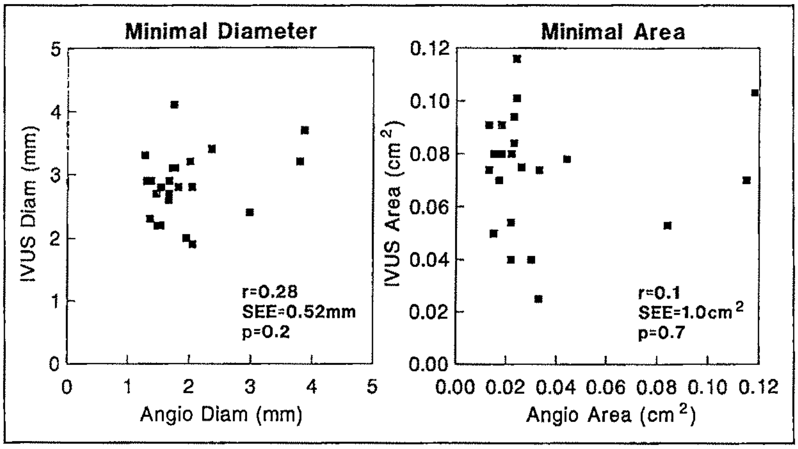

**FIGURE 1. Intravascular ultrasound (IVUS) compared with quantitative angiography (Angio) for determination of lumen diameter (Diam) *(left)* and cross-sectional area *(right)*. SEE = standard error of the estimate.**

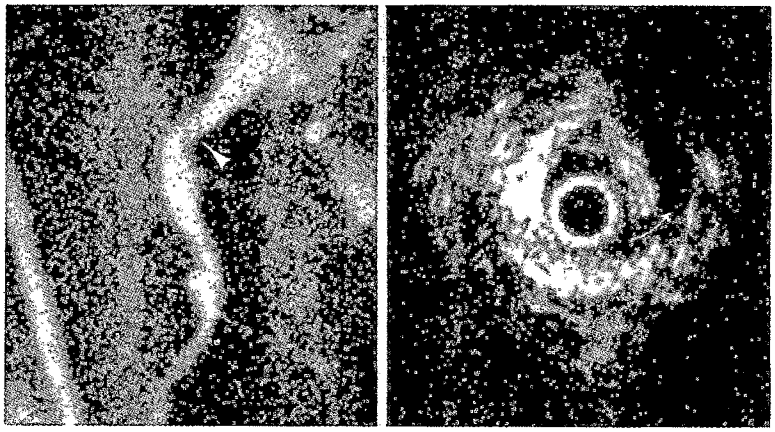

**FIGURE 2. *Left,* right coronary artery angiogram immediately after percutaneous transluminal coronary angioplasty. Haziness is noted at dilation sites, but no obvious dissection *(arrow)*. *Right,* large intimal and medial dissections noted within area of hard plaque.**

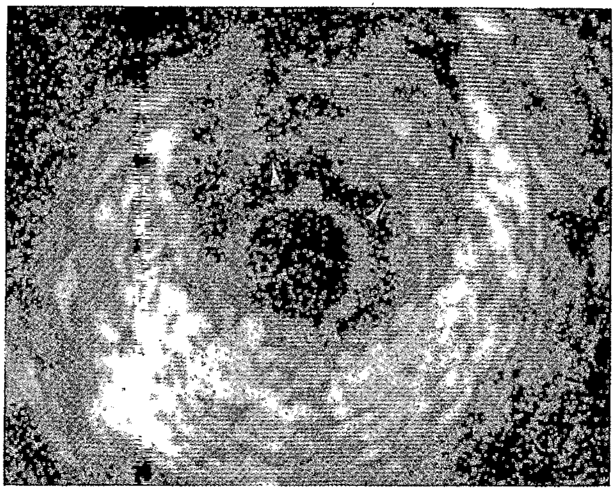

**FIGURE 3. Immediately after 2 passes with excimer laser. Channels and sites of tissue ablation noted within soft plaque *(arrows)*.**

composition and topography were readily identified. Plaque composition was classified as hard or soft based on previously suggested pathologic validated criteria.[3] With the present state of IVUS image quality, more extensive characterization of lesion composition is not validated and may represent an overinterpretation of the images. However, when compared with angiography, the improved lesional descriptors with ultrasound may assist in interventional device selection or prediction of long-term outcome.

Thrombus could not be definitively identified in any patient. Previous studies evaluating thrombus and soft plaque have demonstrated that their ultrasonic characteristics are often similar.[3,6] After peripheral venous angioplasty, IVUS has been demonstrated to be more sensitive than angiography for detection of intraluminal thrombus as well as dissection.[11]

Coronary dissections were more often identified with ultrasound than with cineangiography. It has been well documented in previous studies that angiographic morphologic description, particularly dissection, is a significant predictor of ischemic outcome after PTCA.[9,12] Despite a large dissection noted in the patient in Figure 2, no adverse clinical sequelae were noted acutely, and the patient remains asymptomatic 7 months after PTCA. Whether the improved sensitivity of ultrasound to detect dissection impacts on therapeutic approaches to improve either acute or long-term outcome after angioplasty remains to be determined.

As opposed to previous studies of noninterventional peripheral arterial segments,[2] discordance exists between IVUS and quantitative angiography for determination of postprocedure coronary dimensions. Numerous factors may account for this discrepancy. A previ-

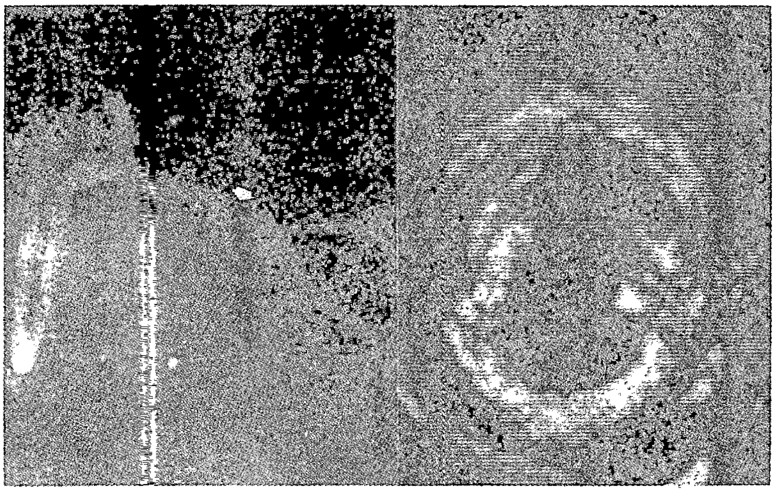

**FIGURE 4. *Left,* left anterior descending coronary artery after directional coronary atherectomy. Note smooth contour of vessel at site of intervention *(arrow)*. *Right,* corresponding intravascular ultrasound image demonstrating channel of excised plaque (7 o'clock) and residual atheroma (12 o'clock).**

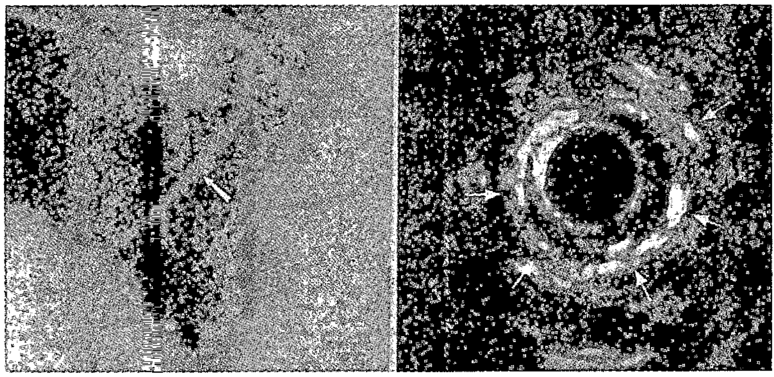

**FIGURE 5. *Left,* after major dissections with percutaneous transluminal coronary angioplasty, stent deployed into mid–left anterior descending coronary artery. Struts are seen poorly with angiography *(arrow)*. *Right,* struts readily visualized without evidence of persistent dissection or luminal compromise.**

ous study in dogs has indicated a poor correlation of ultrasound with angiography after PTCA.[13] These investigators determined that an increase in measured vessel eccentricity accounted for the differences, and that ultrasound may be superior to cineangiography in defining vessel size when lumen shape is distorted. Tobis et al[14] also demonstrated that IVUS and quantitative angiography are discordant after balloon angioplasty. Preliminary data from our laboratory indicate that technical factors inherent to IVUS also contribute to the discordance observed when compared with angiography.[15] Eccentric catheter position, vessel curvature and beam divergence are all potential sources of error in evaluating vessel size and echogenicity. Thus, both angiography and ultrasound may exhibit properties that account for the discrepancies observed in quantitative comparisons.

The size of the population presented in this study does not allow for definitive conclusions regarding the differential acute effects of various interventional technologies. Rather, this study serves to describe the ability of IVUS to provide a more sophisticated and detailed evaluation of coronary interventions. The clinical use of this new imaging modality in the setting of noninvestigational interventions remains to be determined. Although quantitation of postintervention lumen dimensions may have limitations, the qualitative abilities of IVUS should improve the understanding of the acute results and therapeutic impact of new interventional devices when compared with conventional PTCA.

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# Usefulness of Morphologic Parameters in Predicting the Outcome of Coronary Excimer Laser Angioplasty

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**The treatment of complex coronary lesions with conventional balloon angioplasty is associated with a reduced success rate and an increased incidence of complications. To evaluate the influence of lesion morphology on the outcome of coronary excimer laser angioplasty, morphologic parameters of 148 target lesions in 147 consecutive patients were determined. Morphologic analysis included target vessel, involved vessel segment, vessel diameter, minimal lumen diameter, length of the lesion, single discret (concentric/eccentric) or complex lesions (occlusions, bifurcational, tandem or long segmental lesions), American College of Cardiology/American Heart Association Task Force classification, lesion location in curved or straight vessel segments, prestenotic vessel tortuosity and the direction of the laser approach in curved vessels with eccentric lesions. Failure of laser angioplasty occurred in 17 patients because of failed guidewire placement (n = 8), catheter placement (n = 6), or inability to pass the lesion with the laser catheter (n = 3). Successful stand-alone laser angioplasty was achieved in 68 procedures. In 63 interventions additional balloon angioplasty was necessary (n = 60) or stand-alone laser angioplasty was not successful (n = 3).**

**The frequency of complex lesions, particularly total occlusions (p <0.001) and prestenotic vessel tortuosity (p = 0.002) was significantly increased in the group with failed laser attempts. Statistical analysis of the morphologic parameters in successful stand-alone laser interventions compared with combined or unsuccessful interventions revealed no significant difference. These data suggest that failure of laser angioplasty occurs because of low catheter flexibility and the need for guidewire support in treating totally occluded vessels. Furthermore, once the catheter has reached the target, lesion morphology seems to be of minor importance for the success of stand-alone coronary excimer laser angioplasty.**

**(Am J Cardiol 1991;68:1310–1315)**

Excimer laser angioplasty was developed as an alternative or adjunct to balloon angioplasty for treatment of obstructive coronary lesions. Despite the rapid technological progress and improvement of the primary success rates, the acute and long-term results have not shown advantages compared with balloon dilatation.[1-3] However, it is conceivable that because of the different mechanisms of stenosis reduction, there may be advantages in this method that are correlated to specific clinical and morphologic parameters. Coronary excimer laser angioplasty is still in the early phase of clinical evaluation. Although the number of patients treated is limited, exact analysis of the available data is neccessary to determine future strategies. This study addresses the correlation of morphologic parameters of the target vessel to the outcome of coronary excimer laser angioplasty.

## METHODS

**Patients:** The data of 148 procedures of coronary excimer laser angioplasty in 147 patients (123 men and 24 women, mean age 57 ± 9 years) were analyzed. All patients had been previously selected for percutaneous transluminal coronary angioplasty on the basis of symptoms and angiographic findings. All patients had given informed consent to participate in the laser study protocol which had been approved by the local ethical committee. Medication consisted of long-term treatment with acetylsalicylic acid (100 to 500 mg) in all patients, and a combination of calcium antagonists, nitrates and $\beta$ blockers according to the clinical course. The clinical state according to the Canadian Cardiovascular Society functional classification[4] was class I in 8 patients, class II in 69 patients, class III in 53 patients and class IV in 17 patients. One- 2- and 3-vessel disease was present in 92, 37 and 18 patients, consecutively. The target vessel was the left anterior descending artery in 103 interventions, the left circumflex artery in

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**TABLE I** Procedural Parameters of Coronary Excimer Laser Angioplasty*

| | Number of Patients | | |
|---|---|---|---|
| | 1–60 | 61–100 | 101–147 |
| Pulse width | 60 ns | 60 ns | 115 ns |
| Irradiation/intermission | Operator-dependent | 3/2 sec. | 3/2 sec. |
| Catheters (mm) | Prototype 1.4 | 1.3/1.5/1.8 | 1.3/1.5/1.8 |
| No. of fibers (100 μm) | 20 | 20/30/35 | 20/30/35 |
| Energy fluence (mJ/mm$^2$) | 30 ± 5 | 43 ± 14 | 67 ± 19 |
| Mean time of laser energy delivery (sec.) | 123 ± 65 | 117 ± 72 | 51 ± 27 |

*Xenon-chloride excimer laser wavelength 308 nm; repetition rate 20 Hz.

**TABLE II** Morphologic Criteria

Target vessel
Involved vessel segment
Prestenotic lumen diameter
Minimal lumen diameter
Length of the lesion
ACC/AHA Task Force classification
Single discrete/complex lesion
Concentric/eccentric lesion
Tandem stenosis
Long segmental lesion
Total occlusion
Bifurcational lesion
Location in vessel curve
Prestenotic vessel tortuosity
Lasing direction in curved segments

ACC/AHA = American College of Cardiology/American Heart Association.

13 interventions and the right coronary artery in 32 procedures. Excimer laser angioplasty was performed using a commercially available xenon-chloride excimer laser (Max 10, Technolas Inc., Munich, Germany) that emitted light at a wavelength of 308 nm at a repetition rate of 20 Hz. In the first 60 consecutive patients a 1.4 mm catheter was used; for treatment of the following patients we used improved catheters of 1.3, 1.5 and 1.8 mm diameter. In the first 100 consecutive patients the pulse width was 60 ns, which was then subsequently prolonged to 115 ns. The interventional and laser parameters are listed in Table I.

Angioplasty was performed by the transfemoral approach. Heparin 10,000 U, were administered intraarterially. A 9Fr guiding catheter was placed in the ostium of the target vessel and the lesion was visualized after intracoronary application of 0.1 mg nitroglycerin. The laser catheter was advanced over a 0.014-inch flexible guidewire that had been placed in the distal vessel. After the laser catheter was placed at the proximal edge of the stenosis, energy application was started and the catheter was advanced, applying only moderate pressure on the device. Laser energy application was also performed during slow withdrawal of the catheter. The size of the improved catheters was selected according to the prestenotic vessel diameter and stenosis severity that was analyzed in the previous diagnostic coronary angiogram. After each passage of the laser catheter, control angiography was performed to examine the result of ablation. If control angiography after the laser passage revealed a residual lesion of >50% and use of a larger-sized laser catheter was expected to be technically possible, the laser catheters were changed. Criteria to stop laser angioplasty were: (1) a reduction of percent luminal diameter stenosis to <50%; (2) no further improvement of the result after the last laser irradiation cycle; and (3) severe vasospasm (reduction in luminal diameter with vessel occlusion or reduced anterograde flow of contrast medium) or vessel occlusion due to dissection or thrombus formation. Additional balloon angioplasty was performed to improve an unsatisfactory result or to resolve vessel occlusion. After the final irradiation period or the last balloon inflation, vessel patency was controlled by repeat angiograms within 20 minutes. The patients were monitored in the coronary care unit for 24 hours. An early follow-up angiogram of the target vessel was routinely performed within 24 hours after the intervention.

The outcome of laser angioplasty was classified as "failure," "successful stand-alone laser angioplasty," or "unsuccessful stand-alone laser angioplasty." Failure of the intervention was defined as an angioplasty attempt that did not result in a reduction of lesion severity. Success of angioplasty was defined as a reduction of lesion severity to a residual stenosis <50%. In the group classified as unsuccessful stand-alone laser angioplasty, all combined laser and balloon angioplasties and stand-alone laser angioplasties with residual stenosis severity ≥50% were included.

**Morphologic analysis:** All preinterventional coronary angiograms were retrospectively analyzed by a consensus of 2 experienced observers. Quantitative analysis of the prestenotic vessel diameter, minimal lumen diameter and length of the stenosis was performed with a millimeter ruler after tracing the magnified target vessel on transparent paper. Only end-diastolic cine frames were used. The 9Fr guiding catheter was used for calibration of the measurement.

The morphologic criteria used for analysis of the target lesion are listed in Table II. Involved segments were defined to be in the proximal, mid- or distal third of the vessel. The prestenotic vessel diameter was measured as lumen diameter of the lesion-free vessel at the proximal edge of the stenosis. Minimal lumen diameter of the stenosis was measured in the projection that showed the highest degree of stenosis. Length of the stenosis was defined as the distance between 2 points of the diseased segment, beginning and ending, where the lumen was reduced by 20%.[5] All lesions were classified as A, B1, B2 or C according to the American College of Cardiology/American Heart Association Task Force classification[6] using the modification of Ellis et al.[7] Single discrete lesions were defined as lesions $<15$ mm in length[8]; they were additionally classified as concentric (symmetric luminal narrowing in two angiographic projections) or eccentric lesions (asymmetric luminal narrowing in at least 1 angiographic projection). Complex lesions were either longer or tandem lesions (sequence of 2 significant stenoses), long segmental lesions (lesion involving a vessel segment with luminal narrowing of $\geq 20$ mm), total occlusions (Thrombolysis in Myocardial Infarction trial flow grade 0,[9] at least 1-month old by clinical and angiographic findings) or bifurcational lesions (branch vessel of medium or large size originating within the stenosis and being completely surrounded by significant stenotic portions of the lesion to be treated).[8] Criterion for location in a curved vessel was the angle between 2 centerlines through the lumen, from the middle of the stenosis to points 5 cm proximal and distal to the stenosis, drawn and measured on the magnified copy. An angle of $>45°$ indicated a curved vessel. Prestenotic vessel tortuosity was defined as $>2$ bends in the prestenotic vessel. The lasing direction in curves was assessed for eccentric lesions in curved vessels. It was classified as directional if the laser catheter and laser beam headed the lesion and nondirectional if the laser catheter headed the opposite vessel wall (see Figure 1).

**Statistical analysis:** All data were entered in the Statistical Analysis System system for data analysis (SAS Institute Inc., Cary, North Carolina). The frequency of morphologic parameters was compared for the patient group in which a laser attempt failed and the groups with laser ablation in order to reveal predictors for failure. The frequency of morphologic parameters was compared for patients with successful and unsuccessful stand-alone laser angioplasty to find predictors for stand-alone laser success. Univariate as well as multivariate analysis was performed. The univariate analysis for qualitative parameters was performed using the chi-square test for expected counts $>5$ and Fisher's exact test for expected counts $<5$. Quantitative parameters were compared using the U-test.[10] A p value $<0.05$ was considered statistically significant.

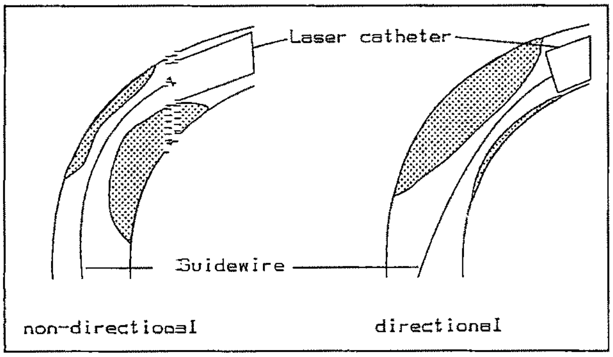

**FIGURE 1. Nondirectional and directional approach of the laser catheter in curved vessel segments with eccentric lesions.**

## RESULTS

**Outcome of laser angioplasty:** It was not possible to place the guidewire in 8 patients, to reach the lesion with the laser catheter in 6 patients, or to pass the stenosis with the catheter in 3 patients. These 17 interventions are summarized in the failure group. A reduction of the target lesion by laser angioplasty could be achieved in 131 coronary arteries. Stand-alone laser angioplasty was successful in 68 procedures. The mean percent stenosis in this group was reduced from 73 ± 12 to 31 ± 14%. Additional balloon angioplasty was neccessary because of an unsatisfactory result ($n = 27$) or owing to complications ($n = 33$) in 60 patients. The interventions resulted in a reduction in stenosis severity from 78 ± 12% to 25 ± 15%. In 1 additional patient a myocardial infarction occurred after stand-alone laser angioplasty and 2 patients had stand-alone laser angioplasty that was initially estimated to be sufficient but did not fulfill the criteria for successful angioplasty using the quantitative analysis. These 63 procedures are summarized in the third group of "not successful stand-alone laser angioplasty."

**Predictors for failure:** The rate for failure in these 148 interventions was 11%. According to the American College of Cardiology/American Heart Association Task Force classification using the modification of Ellis et al,[7] there were 19 type A, 26 type B1, 91 type B2 and 12 type C lesions. Failure of angioplasty occurred in no type A, 1 type B1, 15 type B2, and 1 type C lesion ($p < 0.05$ for A + B1 vs B2 + C lesions). Of all 148 target lesions, 52 were classified as complex lesions (35%). In 13 of these stenoses laser angioplasty failed (25%). The frequency of complex lesions was significantly increased in the failure group ($p < 0.001$). A total number of 15 occlusions had been selected for laser angioplasty (10%); the intervention failed in 7 patients (47%; $p < 0.001$). Laser angioplasty was attempted in 15 patients with long segmental lesions (10%) and was unsuccessful 4 times (27%). The frequency of long segmental lesions showed no significant difference between the failure group and interventions with laser ablation ($p = 0.07$). In 17 target vessels the lesion to be treated was a bifurcational lesion (11%); the intervention failed in 2 cases (11%). Thus, the incidence of failure in these target lesions is identical with the overall failure rate. Prestenotic vessel tortuosity was present in 10 patients (7%). Failure of the intervention occurred in 5 of these patients (50%; $p = 0.002$). The details of all failed laser attempts are listed in Table III.

**Predictors for successful stand-alone laser angioplasty:** In 131 interventions, laser ablation was per-

**TABLE III** Failure of Laser Angioplasty

| Pt. No. | Age (yr) & Sex | CCS | 1-, 2-, or 3-Vessel Disease | Target Artery | Vessel | Segment | Complex Lesion | Failure |
|---|---|---|---|---|---|---|---|---|
| 1 | 52M | 2 | 3 | LAD |  | Proximal | Occlusion | Guidewire placement |
| 2 | 62M | 3 | 2 | LAD |  | Proximal | Occlusion | No passage with catheter |
| 3 | 61M | 3 | 1 | LAD |  | Proximal | Occlusion | Guidewire placement |
| 4 | 44M | 1 | 1 | LC | Curve | Proximal |  | Catheter placement |
| 5 | 67M | 4 | 1 | LAD | Curve | Mid | Bifurcation | Catheter placement |
| 6 | 51M | 3 | 3 | LAD |  | Proximal | Occlusion | Guidewire placement |
| 7 | 63M | 2 | 2 | Right | Tortuosity | Proximal |  | No passage with catheter |
| 8 | 64M | 2 | 2 | LAD | Tortuosity | Proximal |  | Catheter placement |
| 9 | 63M | 2 | 2 | Right | Tortuosity | Mid | Long segmental | Guidewire placement |
| 10 | 56M | 3 | 1 | LC | Curve | Proximal | Occlusion | Guidewire placement |
| 11 | 79M | 2 | 3 | Right | Curve | Proximal | Long segmental | Guidewire placement |
| 12 | 73M | 1 | 3 | Right | Curve | Mid |  | Catheter placement |
| 13 | 44M | 2 | 1 | Right | Curve | Mid | Occlusion | Guidewire placement |
| 14 | 55M | 1 | 2 | LAD | Tortuosity | Mid | Long segmental | Catheter placement |
| 15 | 38F | 3 | 1 | Right |  | Distal | Occlusion | Guidewire placement |
| 16 | 59M | 3 | 2 | LAD | Tortuosity | Mid |  | No passage with catheter |
| 17 | 66M | 4 | 2 | LAD |  | Proximal | Bifurcation | Catheter placement |

CCS = Canadian Cardiovascular Society functional classification; LAD = left anterior descending artery; LC = left circumflex artery.

formed. Stand-alone laser angioplasty was successful in 68 procedures (52%). Morphologic parameters in the groups with successful and unsuccessful stand-alone laser angioplasty and the results of the univariate analysis are listed in Table IV. There was no individual morphologic parameter that correlated with the outcome of laser angioplasty. Logistic regression analysis, performed for sex, age, extent of coronary artery disease, Canadian Cardiovascular Society functional class, target vessel, vessel diameter, lesion length, minimal lumen diameter, occlusion, bifurcation, complex or discrete lesion and lesion type revealed no parameter that was significantly correlated to the outcome with regard to successful or unsuccessful stand-alone laser angioplasty.

Successful stand-alone laser angioplasty was achieved in 23 of 55, 22 of 35 and 23 of 41 interventions in the 3 groups with different procedural parameters. For this analysis the failed laser attempts were excluded. The analysis of the individual procedural parameters showed a significantly lower frequency of successful stand-alone laser procedures (39 of 86) in interventions with an initial energy fluence $<50$ mJ/mm$^2$ compared with procedures with an initial energy fluence $\geq 50$ mJ/mm$^2$ (29 of 45; $p < 0.05$). The frequency of successful stand-alone laser angioplasty was 23 of 55 in procedures with the prototype catheters, 2 of 5 with 1.3 mm, 16 of 27 with 1.5 mm and 27 of 44 with the 1.8 mm catheter (p = not significant). No significant difference was found in patients treated with the identical catheter system and different pulse durations (patients 61 to 100 [60 nanoseconds] versus patients 101 to 147 [115 nanoseconds]) with regard to the stand-alone success rate of coronary excimer laser angioplasty.

**TABLE IV** Predictors for Successful Stand-Alone Laser Angioplasty: Results of Statistical Analysis*

|  | Stand-Alone Laser Angioplasty |  |  |
|---|---|---|---|
|  | Successful (n = 68) | Unsuccessful (n = 63) | p Value |
| LAD/LC/right | 46/7/15 | 48/4/11 | NS |
| Type A/B1/B2/C | 10/12/39/7 | 9/13/37/4 | NS |
| Discrete/complex lesions | 45/23 | 47/16 | NS |
| Curve/straight | 26/42 | 16/47 | NS |
| Mid + distal/proximal segment | 14/54 | 13/50 | NS |
| Length of lesions (mean ± SD) | 7.2 ± 4.7 mm | 7.9 ± 3.7 mm | NS |
| Lumen diameter (mean ± SD) | 2.8 ± 0.7 mm | 2.9 ± 0.7 mm | NS |
| Minimal lumen diameter (mean ± SD) | 0.8 ± 0.3 mm | 0.7 ± 0.4 mm | NS |
| Single discrete lesions |  |  |  |
| Concentric/eccentric | 11/34 | 11/36 | NS |
| Complex lesions |  |  |  |
| Tandem lesions/other | 2/66 | 3/60 | NS |
| Long segmental lesions/other | 7/61 | 4/59 | NS |
| Occlusions/other | 4/64 | 4/59 | NS |
| Bifurcational lesions/other | 11/57 | 5/58 | NS |
| Eccentric lesions in curves |  |  |  |
| Directional/nondirectional | 5/15 | 4/7 | NS |

*Morphologic parameters in patients with successful and unsuccessful stand-alone laser angioplasty.

LAD = left anterior descending; LC = left circumflex artery; NS = not significant; SD = standard deviation.

## DISCUSSION

Morphologic parameters for successful, conventional balloon angioplasty have been previously analyzed.[7,11-15] Throughout the years, the major reason for failure of balloon dilatation was the inability to cross the lesion either with the guidewire in chronic total occlusions or to reach or pass the lesion because of severe vessel tortuosity. However, unsuccessful angioplasty attempts decreased from initially reported rates between 20 and 44%[11–13] to 3.7%[14] within a 10-year period of technical improvement and development of flexible, low-profile balloon catheters. In a recent publication, Ellis et al[7] reported the correlation of stenosis morphology and the outcome of percutaneous transluminal coronary angioplasty in 1,100 angioplasty attempts in patients with multivessel disease. It was documented that procedural success was dependent on the complexity of lesion morphology. Individual parameters were chronic total occlusion, vessel bending, excessive tortuosity and high-grade stenosis severity. Eccentricity, in contradiction to previous publications,[13] had no influence on success of percutaneous transluminal coronary angioplasty. The incidence of major complications is higher in patients with high-grade stenosis severity, complex morphology,[15,16] stenoses at points of vessel angulation[13,17] and long stenoses.[13]

In laser angioplasty, fiberoptic catheter devices are used to transmitt the energy from the light source to the target site in the coronary artery. Device technology reached clinical practicability 2 years ago but is still in progress. As in the early years of balloon angioplasty, the catheters lack flexibility and steerability. Therefore the analysis of the failed laser attempts in this study reveals similar problems as described for the early experience in balloon angioplasty. Individual predictors for failure were prestenotic vessel tortuosity and chronic total occlusion. These data suggest that failure of laser angioplasty is (1) a problem of low flexibility of the catheter devices, and (2) due to the requirement of guidewire support for safe coaxial advancement in treating totally occluded vessels.

There was no morphologic parameter that correlated with a higher rate of successful stand-alone laser angioplasty. The reason for the independence of the angioplasty result in regard to lesion morphology in our study group remains to be clarified. This might be explained in part by the different mechanism of lesion reduction by laser ablation in comparison to conventional balloon dilatation. With excimer laser energy, intravascular atherosclerotic tissue is removed by transformation from the solid to the plasma phase rather than being compressed and disrupted. It has been suggested that this results in a reduction in vessel injury at the site of the intervention.[18,19] This may also explain that success of excimer laser angioplasty was independent of the eccentricity or concentricity of the lesion since catheter size in most patients could be selected according to the vessel diameter. However, success of stand-alone laser angioplasty requires not only sufficient stenosis reduction, but also absence of complications. The considerable incidence of thrombus formation, vasospasm and vessel occlusion after laser angioplasty frequently required additional balloon treatment. This results in a considerable number of unsuccessful stand-alone interventions despite initially successful plaque ablation. However, success rate of stand-alone laser angioplasty in complex lesions, such as long lesions and bifurcational lesions, was comparable to single discrete lesions. Thus, once the catheter reaches the lesion and ablation of the plaque is possible, there is no morphologic parameter that goes along with reduced efficacy or increased risk of complications. This is in contrast to the experience in balloon angioplasty. The use of laser systems could therefore provide a viable alternative in the primary treatment of target lesions, which are associated with lower success rates and higher incidence of complications using conventional balloon angioplasty. The results of this morphologic analysis suggest that laser angioplasty of long segmental lesions and bifurcational lesions should be recommended for controlled prospective clinical studies.

This study is limited by the low frequency of some parameters that reduce the statistical power of the analysis in these subgroups, e.g., the group of eccentric lesions in vessel curves. Furthermore, laser angioplasty is under constant progress, and our study population reflects a heterogenous group with regard to laser and catheter technique as well as investigator experience. It has been documented that increasing energy fluence together with the use of improved catheters resulted in improved rates of successful stand-alone procedures; it is conceivable that with increasing efficacy of tissue ablation and further improvement of catheter technology, the success rate will be further improved. The limitations of the present single-center study underline the need for large scale registrations of the clinical results of coronary excimer laser angioplasty.

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# Early and Late Results of Coronary Angioplasty and Bypass in Octogenarians

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**Early and late results were evaluated for octogenarians undergoing first time revascularization with percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG). The study group consisted of 142 patients with CABG and 53 with PTCA. The groups with PTCA and CABG differed with respect to number of patients with angina class III to IV (92 and 67%, respectively; p <0.001), number with 3-vessel disease (34 and 77%, respectively; p <0.001), presence of left main trunk disease (2 and 24%, respectively; p <0.001) and number with normal or mildly impaired left ventricular function (82 and 65%, respectively; p <0.034). The groups with PTCA and CABG had similar procedural complications, including myocardial infarction (6 and 4%, respectively) and stroke (0 and 4%, respectively). Hospital mortality was low (6% with CABG and 2% with PTCA). Three year survival, excluding hospital mortality, was 87% in patients with CABG and 81% in those with PTCA (p = 0.493). Octogenarians underwent revascularization procedures with relatively low morbidity and mortality. In regard to the excellent long-term survival, "very" elderly patients with severe coronary artery disease should be considered for revascularization despite advanced age.**

**(Am J Cardiol 1991;68:1316–1320)**

The elderly population will increase by an estimated 1.1%/year over the next 20 years.[1] As the number of elderly patients with symptomatic coronary artery disease increases, revascularization procedures will become more frequent. Reports have shown acceptable primary success rates for percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) in patients aged >80 years.[2–7] However, few studies have documented long-term results in those patients and, to our knowledge, there has been only 1 study that compared the 2 treatment strategies.[6–10] To identify the optimal revascularization therapy in the very elderly, we compared the early and late results for PTCA and CABG performed at our institution in patients aged >80 years.

## METHODS

We reviewed the medical records of all patients aged >80 years who underwent first time coronary revascularization at our institution between January 1982 and December 1989. Patients with acute ischemic events or concomitant valvular surgery were excluded. The study population consisted of 142 patients with CABG and 53 with PTCA. The choice of therapy was not randomized.

From each patient's record we documented the presence or absence of previous myocardial infarction, the functional class of angina at the time of revascularization, the presence of unstable angina and concomitant conditions (including diabetes, hypertension and smoking), and any history of cerebral vascular accidents. Coronary angiography documented the extent of disease in all patients. Left ventricular function (determined from ventriculography or echocardiography) was graded as normal or as having mild, moderate or severe dysfunction.

**Definitions of measured variables:** Angina pectoris was graded according to the Canadian Cardiovascular Society guidelines.[11] Unstable angina was defined as new onset (within 8 weeks) or progressive angina, or angina at rest. Significant coronary artery stenosis was defined as ≥50% narrowing in luminal diameter. For patients undergoing PTCA, angiographic success was defined as ≥20% reduction of stenosis, with residual stenosis <50%. Clinical success was defined as angio-

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**TABLE I** Clinical Characteristics of 195 Octogenarians Undergoing Coronary Revascularization

| Characteristic | CABG n (%) | PTCA n (%) | p Value |
|---|---|---|---|
| Sex | | | |
| Men | 87 (61) | 28 (53) | NS |
| Women | 55 (39) | 25 (47) | NS |
| Age (yrs) | 82 ± 2 | 82 ± 2 | NS |
| Systemic hypertension | 75 (53) | 31 (58) | NS |
| Diabetes mellitus | 26 (18) | 11 (21) | NS |
| Peripheral vascular disease | 40 (28) | 19 (36) | NS |
| History of smoking | 58 (41) | 17 (32) | NS |
| Previous myocardial infarction | 69 (49) | 23 (43) | NS |
| Unstable angina | 85 (60) | 30 (57) | NS |
| Angina class | | | |
| CCS1 | 10 (7) | 0 (0) | <0.001* |
| CCS2 | 36 (25) | 4 (8) | |
| CCS3 | 50 (35) | 15 (28) | |
| CCS4 | 46 (32) | 34 (64) | |
| Extent of disease | | | |
| 1 vessel | 3 (2) | 11 (21) | <0.001† |
| 2 vessel | 29 (20) | 23 (43) | |
| 3 vessel | 110 (77) | 18 (34) | |
| Left ventricular function | | | |
| Normal | 53 (37) | 25 (47) | <0.034* |
| Mild dysfunction | 40 (28) | 18 (34) | |
| Moderate dysfunction | 34 (24) | 6 (11) | |
| Severe dysfunction | 15 (11) | 4 (8) | |

*Groups 1 and 2 vs 3 and 4; †groups 1 and 2 vs 3.
CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

**TABLE II** Procedural Variables for 195 Octogenarians Undergoing Coronary Revascularization

| Procedure | n (%) |
|---|---|
| CABG | |
| No. of arteries bypassed | |
| 1 | 5 (4) |
| 2 | 21 (15) |
| 3 | 77 (54) |
| 4 | 39 (27) |
| Internal mammary artery graft | 44 (31) |
| Hospital stay (days) | 18 ± 12 |
| PTCA | |
| No. of arteries dilated | |
| 1 | 30 (57) |
| 2 | 18 (34) |
| 3 | 5 (9) |
| No. of narrowings dilated | |
| 1 | 27 (51) |
| 2 | 18 (34) |
| 3 | 8 (15) |
| Primary success | |
| Angiographic | 82/87 (94%) |
| Clinical | 45/53 (85%) |
| Hospital stay (days) | 9 ± 8 |

Abbreviations as in Table I.

**TABLE III** Complications for 195 Octogenarians Undergoing Coronary Revascularization

| Event | CABG n (%) | PTCA n (%) | p Value |
|---|---|---|---|
| Stroke | 5 (4) | 0 (0) | NS |
| Q-wave myocardial infarction | 5 (4) | 3 (6) | NS |
| Death | 8 (6) | 1 (2) | NS |
| Renal failure | 2 (1) | 2 (4) | NS |
| Sepsis | 4 (3) | 0 (0) | NS |
| Transfusion | 112 (79) | 10 (19) | <0.001 |
| Vascular complications | 3 (2) | 2 (4) | NS |

Abbreviations as in Table I.

graphic success in the absence of in-hospital mortality, myocardial infarction or CABG.[12] Clinical success in patients with multivessel or multilesion disease was defined as successful dilation of the most severe lesion without major complications.

A diagnosis of postoperative myocardial infarction required 2 of the following 3 criteria: (1) presence of new Q waves on electrocardiogram after surgery; (2) increase after surgery in serum creatinine kinase-MB level to >100 IU/liter; or (3) increase after surgery in aspartate aminotransferase level to >100 IU/liter in presence of normal alanine aminotransferase level. Hospital mortality was defined as death occurring within 30 days of surgery or during the same hospitalization.

**Evaluation of long-term results:** Evaluation of long-term results was achieved by direct or telephone contact with patients or immediate relatives. A standard questionnaire was completed on all surviving patients that included specific questions regarding anginal symptoms and activity level.

**Statistical analysis:** Group comparisons of categorical variables were performed using either the chi-square or Fischer's exact test, as appropriate, and *t* tests were used for continuous measures. Values are mean ± standard deviation. A p value <0.05 was considered significant. Survival time was estimated by the method of Kaplan and Meier.[13] Survival distributions were compared using the log-rank test.

## RESULTS

**Baseline characteristics:** The baseline characteristics of both groups are listed in Table I. The groups were similar in regard to age, sex, and presence of unstable angina and related medical illnesses, but differed in functional class, extent of disease, and left ventricular function.

**Results and complications of revascularization:** Results of intervention are listed in Table II. The majority of surgical patients underwent multivessel bypass. In the group with PTCA, intervention was usually limited to the culprit lesion. Hospital stays were longer for patients with CABG than with PTCA (18 ± 12 and 9 ± 8 days, respectively).

**TABLE IV** Late Results and Symptomatic Status for 195 Octogenarians Undergoing Coronary Revascularization

| | CABG<br>n (%) | PTCA<br>n (%) | p Value |
|---|---|---|---|
| Cardiac death | 16 (11) | 8 (15) | NS |
| Myocardial infarction | 1 (1) | 2 (4) | NS |
| Coronary angioplasty | 1 (1) | 2 (4) | NS |
| Coronary bypass | 0 | 4 (8) | <0.005 |
| Status of chest pain | | | |
| Same | 3 (3) | 13 (28) | |
| Better | 101 (93) | 33 (72) | |
| Worse | 4 (4) | 0 (0) | |

Abbreviations as in Table I.

The complications for both groups are listed in Table III. Five patients with CABG had cerebral vascular accidents. Three of these patients had mild transient neurologic dysfunction and 2 had severe disabilities (1 died in the hospital and the other was discharged to an extended care facility). None of the patients with PTCA suffered neurologic complications. Five patients with CABG had a new Q-wave myocardial infarction. An additional 6 patients met enzyme criteria for infarction as previously outlined in Methods. Three patients with PTCA had new Q-wave infarctions. The incidence of periprocedural deaths, renal failure and sepsis was not statistically different between the 2 groups. Surgical patients had a greater number of transfusions, which was expected given the age of the patients. Vascular complications occurred in 2 patients with PTCA (pseudoaneurysms at entry site needing surgical repair) and in 2 with CABG (deep venous thrombosis). In addition, 1 surgical patient had a hematoma of the thigh at the vein harvest site that required surgical drainage. Hospital mortality was low (6% with CABG and 2% with PTCA).

**Long-term results:** Excluding hospital deaths, mean time to follow-up was 40 months (range 0.5 to 88) in the group with CABG and 26 months (range 1.4 to 79) with PTCA. Incidence of cardiac events and status at follow-up are listed in Table IV. There was no statistical difference in the number of patients having subsequent myocardial infarction, PTCA or cardiac death during follow-up. Four patients with PTCA underwent CABG for recurrence of symptoms. Symptomatic status at follow-up was similar between the 2 groups. The majority of patients reported an improvement in their symptoms regardless of the means of revascularization. There was no difference in overall survival between the 2 groups at 36 months. Figure 1 illustrates overall survival excluding hospital mortality. Ten of the 27 (34%) late deaths in the group with CABG were noncardiac. Similar results were seen in the group with PTCA, with 4 of 13 (31%) late deaths being noncardiac. With cardiac death, myocardial infarction or CABG as end points, there was no statistical difference in event-free survival between the 2 groups. Figure 2 shows event-free survival at 36 months excluding hospital mortality.

## DISCUSSION

Only recently have studies begun to address PTCA and CABG in octogenarians. This subject will become increasingly important as the general population ages and as a greater percentage of "very" elderly patients undergo coronary revascularization. Loop et al[14] documented the progressive increase in elderly patients undergoing surgical revascularization over the last decade. Ongoing trials are evaluating the relative merits of PTCA and CABG. However, these trials exclude patients aged >80 years. To determine an optimal treatment strategy for this age group, we compared immediate and long-term results of PTCA and CABG in patients aged >80 years undergoing first time coronary revascularization.

Revascularization of elderly patients may be complicated by a high incidence of extensive coronary artery disease. Kowalchuk et al[15] assessed angiographic findings in octogenarians presenting with symptoms of coronary artery disease and found 3-vessel and left main

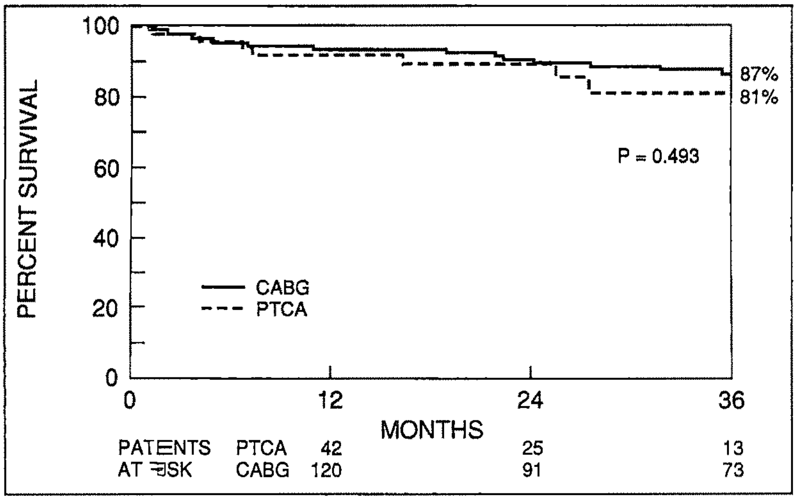

**FIGURE 1. Survival of octogenarians after coronary revascularization (excluding hospital mortality). CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.**

**TABLE V** Summary of Isolated Coronary Revascularization in Octogenarians

| Investigators | n | LMT or 3-Vessel Disease (%) | Functional Class III–IV Angina (%) | Hospital Mortality (%) | Hospital Stay (days) | Long-Term Survival (time to follow-up) | Functional Class I or II at Follow-Up (%) |
|---|---|---|---|---|---|---|---|
| PTCA | | | | | | | |
| Jeroudi et al[7] | 54 | 81 | 91 | 4 | 3 | 80% (3 yrs) | 93 |
| Kern et al[3] | 21 | 61 | 91 | 19 | | Not determined | |
| Little et al[2] | 50 | | | 10 | | 88% (1 yr)* | 92 |
| Rich et al[4] | 22 | 14 | 100 | 0 | | 91% (11 mos) | |
| Good et al[20] | 75 | | >57 | 3.5 | | 75% (2 yrs) | 82 |
| Braunstein et al[10] | 36 | | 100 | 3 | | 83% (18.8 mos) | |
| CABG | | | | | | | |
| Mullany et al[16] | 159 | 86 | 97 | 10.7 | 14.6 | 71% (5 yrs) | 89 |
| Ware et al[17] | 158 | | 83 | 9.6 | | 66% (5 yrs) | |
| Kowalchuk et al[9] | 40 | | | 13 | | 81% (25 mos)* | |
| Khan et al[8] | 150 | | >75 | 4.7 | | 65% (5 yrs)* | |
| Edmunds et al[18] | 41 | | | 24 (@90 days) | | 88% (40.9 mos)* | 98 |
| Braunstein et al[10] | 29 | | 100 | 10 | | 83% (18.8 mos) | |

*Excluding hospital mortality.
LMT = left main trunk; other abbreviations as in Table 1.

disease in 70% of patients. Other studies confirm the high prevalence of 3-vessel disease in octogenarians referred for therapy.[3,7,16] Extensive coronary artery disease not only influences a patient's suitability for revascularization, but also results in selection bias for the type of procedure performed. Patients with 3-vessel or left main trunk disease, or poor left ventricular function are more likely to be referred for CABG. Indeed, we found that the octogenarians undergoing CABG in our series had a higher incidence of 3-vessel and left main trunk diseases, along with worse left ventricular function compared with those undergoing PTCA. This selection bias makes direct comparison of the 2 groups difficult. However, despite their worse status before surgery, survival in patients with CABG was the same as that in those with PTCA.

Significant morbidity, including myocardial infarction and stroke, is more frequent in elderly patients after coronary revascularization. This must be taken into account when referring elderly patients for therapy. Up to 5% of elderly patients can be expected to have myocardial infarction or stroke after surgery.[4,7,17] In our series, no patient with PTCA had a cerebral vascular accident, and only 2 of the surgical patients had persistent neurologic deficits. The incidence of myocardial infarction was also low (4% with CABG and 6% with PTCA). These findings suggest that contrary to earlier reports, selected octogenarians can undergo revascularization with a relatively low risk of morbidity.

Table V summarizes the results of previous studies of isolated coronary revascularization in octogenarians. In most cases, patients had severe coronary disease and functional class III to IV angina. Hospital mortality ranged from 0 to 24%. Variability in reported mortality may be due, in part, to differences in patient populations. Typically, hospital mortality is approximately 5 to 10% in octogenarians. Several risk factors have been shown to increase operative mortality in elderly patients, including: increasing age;[14] female sex;[14] unstable angina;[16] diabetes;[17] smoking[14]; and worsening left ventricular function or functional class.[8,17,18] The studies listed in Table V show similar hospital mortality

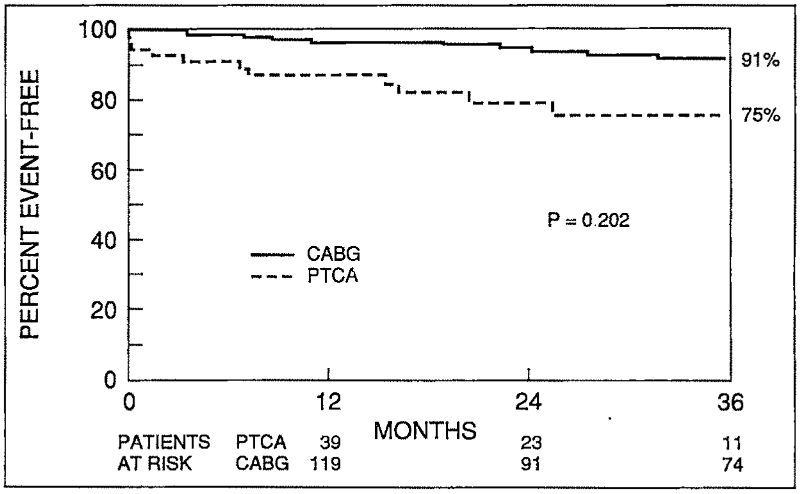

**FIGURE 2. Survival of octogenarians after coronary revascularization (free of cardiac death, myocardial infarction or coronary artery bypass grafting [CABG] [excluding hospital mortality]). PTCA = percutaneous transluminal coronary angioplasty.**

irrespective of the type of revascularization. Hospital mortality in our series (2% with PTCA and 6% with CABG) compares favorably with the studies listed.

In our patients, overall survival at 3 years was approximately 83% whether revascularized with PTCA or CABG. Average life expectancy for 80-year-old men and women is 5.9 and 8.8 years, respectively.[19] At least 1 other study has shown near normal survival for octogenarians after surgery.[14] Approximately one third of late deaths in both groups were noncardiac, presumably a reflection of the high frequency of concomitant illnesses. The most frequent cause of noncardiac death was malignancy.

In addition to long-term survival, symptomatic status after surgery is also important. Typical indexes of functional status, such as number of patients returning to employment, may not be applicable in the very elderly. Previous studies, including those listed in Table V, have documented marked improvement in angina functional class after surgery.[2,7,16,18,20] With angina as an endpoint, the majority of our patients reported improvement in their symptoms after revascularization.

**Conclusion:** We found that both PTCA and CABG in octogenarians resulted in low hospital mortality, effective relief of symptoms, and excellent long-term survival. Octogenarians with severe coronary artery disease and advanced symptoms should be considered for revascularization despite advanced age.

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# Effects of Increased Heart Rate and Sympathetic Tone on Intraventricular Electrogram Morphology

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**Electrogram pattern recognition by way of morphologic analysis has been proposed as a technique that may improve discrimination of ventricular tachycardia from sinus rhythm by antitachycardia devices. The potential impact that increases in heart rate and sympathetic tone could have on such techniques, however, has not been previously determined. A comparative study was undertaken to quantify possible changes in ventricular electrogram morphology using correlation waveform, area of difference, and amplitude analyses in 6 patients during atrial overdrive pacing at cycle lengths of 600 and 400 ms (group A), in 13 patients during infusions of physiologic doses of epinephrine (group B), and in 20 patients undergoing infusions of isoproterenol (group C). Four patients were in both groups A and B. A bipolar intraventricular template of cardiac depolarization during sinus rhythm at rest was compared with depolarization during subsequent passages of sinus rhythm at rest and subsequently increased heart rate.**

**In 36 of 39 patients, waveform configuration as assessed by correlation waveform analysis remained relatively stable during atrial overdrive pacing, epinephrine infusion, and isoproterenol infusion when compared with sinus rhythm at rest. The correlation value did not fall below 0.950 in any patient. Area of difference values for the same 36 patients changed by an average of 6 and 37% during atrial overdrive pacing at cycle lengths of 600 and 400 ms intervals, respectively, by 3% during epinephrine infusion, and by 17% during isoproterenol infusion. In these same patients, there was an average change in electrogram amplitude of −1% during atrial overdrive pacing at 600 ms, 26% during pacing at 400 ms, −1% during epinephrine infusion, and 12% during isoproterenol infusion.**

**Little or no correlation was found between relative changes of amplitude and changes of correlation coefficient during any intervention. However, changes in amplitude and changes in area of difference exhibited weak to moderate correlation during infusion of epinephrine and isoproterenol. Despite some amplitude variation, overall waveform morphology remains relatively constant during increases in heart rate with or without concurrent changes in sympathetic tone. These findings suggest that heart rate increases are unlikely to confound time-domain detection schemes used in antitachycardia devices.**

**(Am J Cardiol 1991;68:1321–1328)**

A variety of methods for analyzing intracardiac electrograms have been proposed for arrhythmia detection by antitachycardia devices. Such methods include rate onset and stability,[1] multichannel timing analysis,[2-4] gradient pattern detection,[5,6] analysis of arrhythmia frequency spectra,[7-9] area of difference,[10,11] and correlation waveform analysis.[12-17] However, with the exception of preliminary investigations by Paul[18] and Rosenheck[19] and their co-workers in humans, and Tomaselli et al[20] in dogs, most studies to date have been performed on electrocardiographic signals recorded from patients in a resting state. Whether the results of waveform analysis techniques designed to recognize abnormal ventricular activation might be affected by increases in heart rate alone or by accelerations in heart rate due to changes in sympathetic tone has not been determined with certainty. This study examined the effects on intraventricular electrogram morphology caused by (1) increases in heart rate alone during atrial overdrive pacing, and (2) changes in heart rate and sympathetic tone due to intravenous infusions of either a $\beta$ or a combined $\alpha$ and $\beta$ agonist.

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## METHODS

**Patient group:** Thirty-five patients were entered into this study after giving informed consent and were categorized into 3 groups. Group A included 6 patients (3 women aged 40 ± 16 years and 3 men aged 49 ± 18 years) studied during atrial overdrive pacing rates of 100 beats/min (600 ms intervals) and 150 beats/min (400 ms intervals). Group B consisted of 13 patients (4 from group A and 9 additional) (5 women aged 44 ± 13 years and 8 men aged 50 ± 14 years) undergoing epinephrine infusion. Group C was composed of 20 patients (9 women aged 58 ± 16 years and 11 men aged 51 ± 16 years) studied during infusion of isoproterenol. No patient was receiving antiarrhythmic drugs at the time of the electrophysiologic study. Nineteen patients had no prior evidence of heart disease, 13 had coronary artery disease, 1 had a previous myocardial infarction, 1 had mitral valve prolapse and 1 had myotonic dystrophy.

**Electrophysiology study:** Patient data were acquired from bipolar electrode catheters with 1 cm interelectrode spacing during elective cardiac electrophysiologic studies as described previously.[14] In the resting state, a 12-lead electrocardiogram was recorded during sinus rhythm for baseline measurement purposes. The patient was then either stimulated with atrial overdrive pacing at a cycle length of 600 ms followed by pacing at intervals of 400 ms (group A), treated with a physiologic dose[21] of an $\alpha$ and $\beta$ agonist, epinephrine (50 ng/kg/min) (group B), or given a clinical infusion[22] of a pure $\beta$ agonist, isoproterenol (2 $\mu$g/min) (group C).

Electrocardiograms from 2 or 3 surface leads (from I, II, III and $V_1$), a high right atrial lead, and a right ventricular apical lead were amplified through either a Siemens Mingograf-7 (Siemens-Elema, Solna, Sweden) or a Honeywell Electronics-for-Medicine (Electronics-for-Medicine, Pleasantville, New York) data amplifier. Each channel was recorded with wide-band filter settings of 0.5 to 500 Hz (Siemens Mingograf-7) or 1 to 500 Hz (Honeywell Electronics-for-Medicine), and outputs were connected to a Hewlett-Packard 3968A FM tape recorder (Hewlett-Packard, San Diego, California). Signals were recorded on magnetic tape at a speed of 3¾ inches/s with an effective bandwidth of 0 to 1,250 Hz. All recordings were obtained while patients were lying supine.

**Intraventricular electrogram analysis:** Intraventricular electrograms were digitized at a sampling rate of 1,000 Hz using a personal computer. Two separate passages of sinus rhythm before clinical intervention were digitized; the first was used for template generation and the second for baseline analysis. Additional data were digitized from each pacing passage for group A patients, from a passage during epinephrine infusion for group B patients, and from a passage during isoproterenol infusion for group C patients. The length of each digitized passage varied from 10 to 30 seconds.

The average cycle length of the control sinus rhythm passage and the passage during clinically accelerated heart rate was determined for each patient. The average decrease in absolute cycle length for each group was evaluated by a 2-tailed, paired Student's *t* test, and a p value was derived to represent the overall significance of the decrease.

To perform electrogram analysis and quantitate the similarity or dissimilarity between ventricular depolarizations, an appropriate window of electrogram depolarization for analysis was chosen for each patient. The window was selected from a typical depolarization of the first sinus rhythm passage and, in order to exclude acute injury current during repolarization, included ventricular depolarization only by beginning at the first deviation from baseline and ending at the first evidence of repolarization. The initial window size was imposed on all subsequent analysis for the same patient.

A representative, signal-averaged template of the patient's normal sinus rhythm was compared individually with each ventricular depolarization of the second baseline passage of sinus rhythm using correlation waveform, area of difference, and amplitude analyses. Accurate alignment of the ventricular depolarization under analysis was effected by a sliding window method[14] to compensate for misaligned trigger points. The template was then compared in a similar manner with every depolarization of the accelerated heart rate passage.

**Correlation waveform analysis:** The correlation coefficient[12–17] is a metric between ± 1 which represents the morphologic similarity between 2 waveforms. It is a statistically based measure that is independent of amplitude and baseline variations and measures only relative shape differences between the template and the waveform being examined. This technique was used to compare the template depolarization with each depolarization from the control passage of sinus rhythm based on a previously published formula[16] and correlation coefficients were averaged to yield a mean ± standard deviation (CWA:SR). The average ± standard deviation of correlation coefficients for each passage during subsequent intervention (CWA:INT) was also computed. Because correlation values of sinus rhythm were consistently high and approached 1, we defined the percent change of correlation coefficient from the control sinus rhythm passage to the passage during intervention (Δ:CWA) according to the following formula:

$$\Delta\text{:CWA} = \left(\frac{\text{CWA:INT} - \text{CWA:SR}}{\text{CWA:SR}}\right) \times 100\%.$$

**Area of difference analysis:** Area of difference[10,11] directly measures the absolute amplitude difference be-

**TABLE I** Results of Morphologic Analysis of Atrial Overdrive Pacing at 600 ms Intervals

| Pt. No. | CWA:SR | CWA:600 | AOD:SR (%) | AOD:600 (%) | AMP:SR (%) | AMP:600 (%) | Δ:CWA (%) | Δ:AOD (%) | Δ:AMP (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.996 ± 0.003 | 0.995 ± 0.003 | 7 ± 3 | 34 ± 1 | 1 ± 2 | 8 ± 11 | −0.1 | +27 | +7 |
| 6 | 0.994 ± 0.001 | 0.993 ± 0.001 | 16 ± 5 | 5 ± 1 | −9 ± 6 | 5 ± 11 | −0.1 | −11 | +14 |
| 8 | 0.998 ± 0.001 | 0.994 ± 0.003 | 6 ± 2 | 11 ± 3 | 1 ± 2 | −6 ± 19 | −0.1 | +5 | −7 |
| 10 | 0.997 ± 0.001 | 0.996 ± 0.002 | 8 ± 3 | 18 ± 8 | 1 ± 4 | −12 ± 2 | −0.1 | +10 | −13 |
| 34 | 0.988 ± 0.007 | 0.989 ± 0.013 | 12 ± 3 | 15 ± 4 | 1 ± 9 | 5 ± 6 | +0.1 | +3 | +4 |
| 35 | 0.994 ± 0.001 | 0.988 ± 0.004 | 13 ± 2 | 17 ± 5 | 2 ± 14 | −6 ± 13 | −0.6 | +4 | −8 |

AMP:SR = average amplitude during sinus rhythm; AMP:600 = average amplitude during atrial overdrive pacing at cycle length of 600 ms; AOD:SR = average area of difference during sinus rhythm; AOD:600 = average area of difference during pacing at 600 ms; CWA:SR = average correlation coefficient during sinus rhythm; CWA:600 = average correlation coefficient during pacing at 600 ms; Δ:AMP = change in peak-to-peak amplitude; Δ:AOD = change in area of difference; Δ:CWA = change in correlation coefficient.

**TABLE II** Results of Morphologic Analysis of Atrial Overdrive Pacing at 400 ms Intervals

| Pt. No. | CWA:SR | CWA:400 | AOD:SR (%) | AOD:400 (%) | AMP:SR (%) | AMP:400 (%) | Δ:CWA (%) | Δ:AOD (%) | Δ:AMP (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.996 ± 0.003 | 0.979 ± 0.004 | 7 ± 3 | 53 ± 2 | 1 ± 2 | 8 ± 2 | −1.7 | +46 | +7 |
| 6 | 0.994 ± 0.001 | 0.995 ± 0.001 | 16 ± 5 | 30 ± 4 | −9 ± 6 | 41 ± 10 | +0.1 | +14 | +50 |
| 8 | 0.998 ± 0.001 | 0.987 ± 0.005 | 6 ± 2 | 20 ± 8 | 1 ± 2 | 7 ± 5 | −1.1 | +14 | +6 |
| 10 | 0.997 ± 0.001 | 0.988 ± 0.002 | 8 ± 3 | 78 ± 13 | 1 ± 4 | 19 ± 16 | −0.9 | +70 | +18 |
| 34 | 0.988 ± 0.007 | 0.952 ± 0.007 | 12 ± 3 | 73 ± 14 | 1 ± 9 | 50 ± 15 | −3.6 | +61 | +49 |
| 35 | 0.994 ± 0.001 | 0.981 ± 0.006 | 13 ± 2 | 28 ± 9 | 2 ± 14 | 29 ± 18 | −1.3 | +15 | +27 |

AMP:400 = average amplitude during atrial overdrive pacing at cycle length of 400 ms; AOD:400 = average area of difference during pacing at 400 ms; CWA:400 = average correlation coefficient during pacing at 400 ms; other abbreviations as in Table I.

tween associated sample points of the template and the waveform under analysis and is dependent on fluctuations in amplitude and baseline. To eliminate the effects of direct-current offset, a variation on this formulation that normalizes the absolute area of difference by the total area of the template has been derived.[16] With use of this format, the area of difference was computed between the template depolarization and each depolarization of both the control passage of sinus rhythm and that during subsequent intervention, and these values were averaged to yield a mean ± standard deviation for each passage (AOD:SR and AOD:INT). The percent change of the area of difference from the control passage of sinus rhythm to the passage during intervention (Δ:AOD) was calculated as follows:

$$\Delta\text{:AOD} = \text{AOD:INT} - \text{AOD:SR}$$

**Amplitude analysis:** The difference in peak-to-peak electrogram amplitude due to intervention was also analyzed for each patient. The absolute peak-to-peak amplitude of the template depolarization ($PP_{tmp}$) and each depolarization of the baseline sinus rhythm passage ($PP_{dep}$) was determined, and a normalized value representing the difference of amplitude between these depolarizations ($AMP_{dep}$) was calculated as follows:

$$\text{AMP}_{dep} = \frac{\text{PP}_{dep} - \text{PP}_{tmp}}{\text{PP}_{tmp}} \times 100\%.$$

The normalized difference of amplitude values for all depolarizations of the baseline sinus rhythm passage were averaged to yield a mean ± standard deviation for the passage (AMP:SR). The average ± standard deviation of the difference of amplitude during subsequent intervention (AMP:INT) was computed similarly. Finally, the percent change of normalized difference of amplitude from the control passage of sinus rhythm to the passage during intervention (Δ:AMP) was calculated as follows:

$$\Delta\text{:AMP} = \text{AMP:INT} - \text{AMP:SR}$$

**Scatter diagrams:** Scatter diagrams of (1) the change of amplitude versus the change of correlation coefficient, and (2) the change of amplitude versus the change of area of difference were plotted for each intervention. When a linear probabilistic model was deemed appropriate (i.e., when the points tended to cluster about a straight line and when ≥10 data points were available), linear regression analysis[23] was used to obtain an equation of the estimated regression line. In each case, the change in amplitude was chosen to be the independent variable, and a best fit line to the data and the corresponding sample correlation coefficient, r, were determined.

## RESULTS

Data from correlation waveform, area of difference and amplitude analyses during atrial overdrive pacing, infusions of epinephrine, and infusions of isoproterenol are summarized in Tables I to IV and are illustrated for 3 patients in Figures 1 to 3. The width of the depolarization analysis window for the 35 patients of this study ranged from 29 to 100 ms (mean 51.2 ± 14.8).

**Cycle length:** The sinus rhythm cycle length for group A patients was 765 ± 99 ms. Atrial overdrive pacing at 600 ms intervals decreased the cycle length by 161 ms (p <0.02) and pacing at 400 ms intervals decreased the cycle length by 363 ms (p <0.0005). Epinephrine infusion decreased the mean sinus rhythm cycle length of 773 ± 138 ms for group B patients by 88 ms (p <0.005), and isoproterenol infusion decreased

**TABLE III** Results of Morphologic Analysis of Epinephrine Infusion

| Pt. No. | CWA:SR | CWA:EPI | AOD:SR (%) | AOD:EPI (%) | AMP:SR (%) | AMP:EPI (%) | Δ:CWA (%) | Δ:AOD (%) | Δ:AMP (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.996 ± 0.003 | 0.996 ± 0.003 | 7 ± 3 | 14 ± 2 | 1 ± 2 | 8 ± 8 | 0.0 | +7 | +7 |
| 2 | 0.999 ± 0.001 | 0.998 ± 0.001 | 11 ± 3 | 11 ± 3 | 1 ± 13 | −3 ± 10 | −0.1 | 0 | −4 |
| 3 | 0.992 ± 0.005 | 0.983 ± 0.006 | 13 ± 3 | 16 ± 2 | −1 ± 7 | −8 ± 9 | −0.9 | +3 | −7 |
| 4 | 0.994 ± 0.005 | 0.983 ± 0.007 | 12 ± 5 | 15 ± 2 | 2 ± 9 | 1 ± 3 | −1.1 | +3 | −1 |
| 5 | 0.996 ± 0.001 | 0.980 ± 0.003 | 9 ± 2 | 17 ± 2 | −1 ± 3 | 1 ± 8 | −1.6 | +8 | +2 |
| 6 | 0.994 ± 0.001 | 0.990 ± 0.002 | 16 ± 5 | 13 ± 2 | −9 ± 6 | −5 ± 5 | −0.4 | −3 | +4 |
| 7 | 0.993 ± 0.002 | 0.989 ± 0.001 | 11 ± 2 | 16 ± 2 | 6 ± 6 | 6 ± 36 | −0.4 | +5 | 0 |
| 8 | 0.998 ± 0.002 | 0.993 ± 0.004 | 6 ± 2 | 12 ± 3 | 1 ± 2 | 5 ± 4 | −0.5 | +6 | +4 |
| 9 | 0.982 ± 0.012 | 0.982 ± 0.009 | 44 ± 25 | 21 ± 7 | 18 ± 29 | 2 ± 23 | 0.0 | −23 | −16 |
| 10 | 0.997 ± 0.001 | 0.997 ± 0.001 | 8 ± 3 | 15 ± 6 | 1 ± 4 | 7 ± 6 | 0.0 | +7 | +6 |
| 11 | 0.996 ± 0.002 | 0.975 ± 0.009 | 18 ± 6 | 26 ± 5 | 5 ± 14 | −8 ± 14 | −2.1 | +8 | −13 |
| 12 | 0.994 ± 0.003 | 0.982 ± 0.008 | 12 ± 2 | 29 ± 9 | 3 ± 3 | 12 ± 13 | −1.2 | +17 | +9 |
| 13* | 0.982 ± 0.011 | 0.890 ± 0.018 | 17 ± 6 | 39 ± 5 | −8 ± 4 | −11 ± 19 | −9.4 | +23 | −3 |

*This patient had a paradoxical change of correlation coefficient and is not included in the statistical analyses.
AMP:EPI = average amplitude during epinephrine infusion; AOD:EPI = average area of difference during epinephrine infusion; CWA:EPI = average correlation coefficient during epinephrine infusion; other abbreviations as in Table I.

**TABLE IV** Results of Morphologic Analysis of Isoproterenol Infusion

| Pt. No. | CWA:SR | CWA:ISO | AOD:SR (%) | AOD:ISO (%) | AMP:SR (%) | AMP:ISO (%) | Δ:CWA (%) | Δ:AOD (%) | Δ:AMP (%) |
|---|---|---|---|---|---|---|---|---|---|
| 14 | 0.995 ± 0.003 | 0.967 ± 0.030 | 19 ± 8 | 34 ± 11 | −33 ± 10 | −24 ± 15 | −2.8 | +15 | +9 |
| 15 | 0.997 ± 0.002 | 0.994 ± 0.005 | 7 ± 2 | 12 ± 2 | 1 ± 4 | −2 ± 6 | −0.3 | +5 | −3 |
| 16 | 0.996 ± 0.022 | 0.973 ± 0.015 | 10 ± 4 | 54 ± 31 | −1 ± 5 | 8 ± 23 | −2.3 | +44 | +9 |
| 17 | 0.996 ± 0.002 | 0.997 ± 0.001 | 19 ± 5 | 23 ± 5 | 13 ± 15 | 25 ± 16 | +0.1 | +4 | +12 |
| 18 | 0.996 ± 0.002 | 0.991 ± 0.002 | 15 ± 5 | 53 ± 13 | 2 ± 10 | 23 ± 13 | −0.5 | +38 | +21 |
| 19 | 0.996 ± 0.003 | 0.995 ± 0.003 | 10 ± 4 | 14 ± 3 | −2 ± 3 | 8 ± 4 | −0.1 | +4 | +10 |
| 20 | 0.995 ± 0.003 | 0.975 ± 0.002 | 11 ± 2 | 43 ± 1 | −4 ± 2 | −4 ± 6 | −2.0 | +32 | 0 |
| 21 | 0.996 ± 0.002 | 0.997 ± 0.001 | 11 ± 5 | 11 ± 5 | −9 ± 7 | 3 ± 11 | +0.1 | 0 | +12 |
| 22 | 0.967 ± 0.012 | 0.953 ± 0.007 | 39 ± 17 | 62 ± 17 | 29 ± 26 | 48 ± 14 | −1.5 | +23 | +19 |
| 23 | 0.998 ± 0.002 | 0.981 ± 0.016 | 6 ± 2 | 26 ± 8 | 0 ± 3 | 17 ± 10 | −1.7 | +20 | +17 |
| 24 | 0.997 ± 0.002 | 0.997 ± 0.001 | 5 ± 2 | 22 ± 4 | 0 ± 4 | 10 ± 6 | 0.0 | +17 | +10 |
| 25 | 0.997 ± 0.002 | 0.996 ± 0.002 | 15 ± 5 | 12 ± 5 | −1 ± 6 | −6 ± 6 | −0.1 | −3 | −5 |
| 26 | 0.996 ± 0.001 | 0.996 ± 0.002 | 15 ± 7 | 48 ± 13 | −3 ± 14 | 53 ± 15 | 0.0 | +33 | +56 |
| 27 | 0.990 ± 0.003 | 0.962 ± 0.009 | 24 ± 8 | 57 ± 2 | −10 ± 11 | −1 ± 7 | −2.8 | +33 | +9 |
| 28 | 0.996 ± 0.002 | 0.993 ± 0.002 | 13 ± 5 | 14 ± 4 | 0 ± 8 | 4 ± 3 | −0.3 | +1 | +4 |
| 29 | 0.996 ± 0.004 | 0.996 ± 0.002 | 10 ± 5 | 12 ± 2 | −2 ± 12 | 26 ± 11 | 0.0 | +2 | +28 |
| 30 | 0.990 ± 0.005 | 0.961 ± 0.039 | 18 ± 3 | 50 ± 20 | −10 ± 23 | −6 ± 8 | −3.0 | +32 | +4 |
| 31 | 0.995 ± 0.002 | 0.994 ± 0.002 | 10 ± 5 | 15 ± 5 | −1 ± 5 | 4 ± 4 | −0.1 | +5 | +5 |
| 32* | 0.968 ± 0.012 | 0.759 ± 0.003 | 24 ± 5 | 63 ± 9 | 7 ± 5 | 130 ± 8 | −21.6 | +39 | +123 |
| 33* | 0.992 ± 0.004 | 0.786 ± 0.009 | 19 ± 9 | 261 ± 8 | −1 ± 9 | 12 ± 7 | −20.8 | +242 | +13 |

*These patients had paradoxical changes in correlation coefficients and were not included in the statistical analyses.
AMP:ISO = average amplitude during isoproterenol infusion; AOD:ISO = average area of difference during isoproterenol infusion; CWA:ISO = average correlation coefficient during isoproterenol infusion; other abbreviations as in Table I.

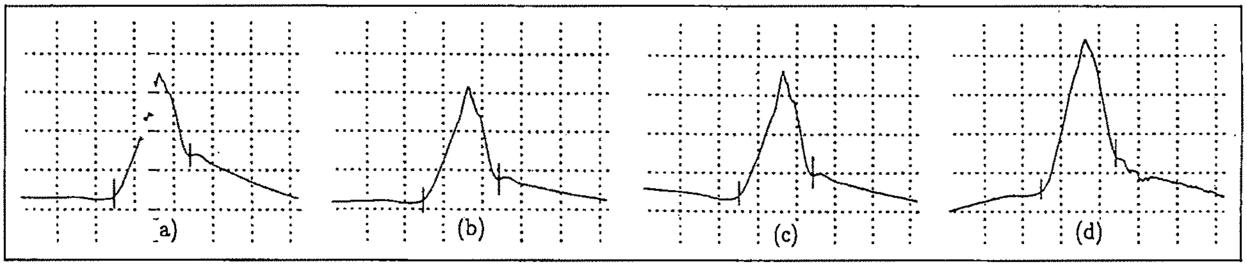

**FIGURE 1. Electrograms from patient 6 during atrial overdrive pacing at rates of 600 and 400 ms. A signal-averaged intraventricular depolarization is shown from a passage during *(a)* sinus rhythm for template construction, *(b)* a subsequent control passage of sinus rhythm, *(c)* pacing at 600 ms, and *(d)* pacing at 400 ms. The figures are plotted at a paper speed of 200 mm/s with a gain of 100 mV/mm. The 51 ms analysis window of electrogram depolarization is marked by *vertical bars* on the original 180 ms window. Although the change in correlation coefficient was small during pacing at both 600 and 400 ms (−0.1 and +0.1%), larger changes in area of difference (−11 and +14%) and amplitude (+14 and +50%) occurred.**

the sinus rhythm cycle length of 797 ± 151 ms for group C patients by 231 ms ($p < 0.0001$). With the exception of 1 patient (no. 13) no consistent relationship could be found between the change in cycle length due to any intervention and the change of correlation coefficient, area of difference, or amplitude of the electrogram.

**Correlation waveform analysis:** For 6 of 6 group A patients (100%), the change in correlation coefficient during pacing at 600 ms intervals ranged from −0.6 to +0.1% and averaged −0.2%. During pacing at a cycle length of 400 ms, the change in correlation coefficient ranged from −3.6 to +0.1% and averaged −1.4%.

The change in correlation coefficient for 12 of 13 patients (92%) during epinephrine infusion (group B) ranged from −2.1 to 0% and averaged −0.7%. A large, unexplained change of correlation coefficient (9.4%) was seen in 1 patient (no. 13).

The change in correlation coefficient for 18 of 20 patients (90%) during isoproterenol infusion (group C) ranged from −2.8 to +0.1% and averaged −1.0%. Two group C patients (nos. 32 and 33) had a paradoxical change of correlation coefficient of −20.8 and −21.6%.

**Area of difference analysis:** For patients in group A, the change of area of difference during atrial overdrive pacing at a cycle length of 600 ms ranged from −11 to +27% and averaged +6%. Pacing at a cycle length of 400 ms produced a change in area of difference that ranged from +14 to +70% and averaged +37%.

For the 12 of 13 group B patients with stable correlation coefficients during epinephrine infusion, the change in area of difference ranged from −23 to +17% and averaged +3%.

For the 18 of 20 group C patients with stable correlation coefficients during isoproterenol infusion, the change in area of difference ranged from −3 to +44% and averaged +17%.

**Amplitude analysis:** The change in amplitude for group A patients during atrial overdrive pacing at a cycle length of 600 ms ranged from −13 to +14% and averaged −1%. The change in amplitude during pacing at a cycle length of 400 ms ranged from +6 to +50% and averaged +26%.

For the 12 patients from group B with stable correlation coefficients during epinephrine infusion, the change in amplitude ranged from −16 to +9% and averaged −1%.

For the 18 group C patients with stable correlation coefficients during isoproterenol infusion, the change in amplitude ranged from −5 to +56% and averaged +12%.

**Scatter diagrams:** Figures 4 and 5 illustrate the scatter plots of change of amplitude versus change of correlation coefficient and change of amplitude versus

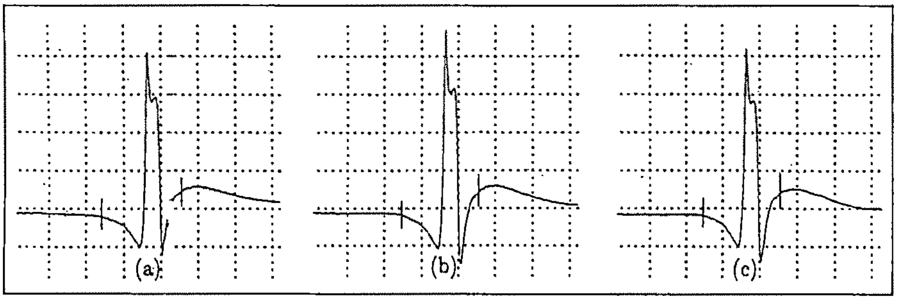

**FIGURE 2. Electrograms from patient 9 during infusion of epinephrine. A signal-averaged intraventricular depolarization is shown from *(a)* passage of sinus rhythm for template construction, *(b)* a subsequent control passage of sinus rhythm, and *(c)* passage during epinephrine infusion. The figures are plotted at a paper speed of 200 mm/s with a gain of 50 mV/mm. The 53 ms analysis window of electrogram depolarization is marked on the original 180 ms window. This patient had no change in correlation coefficient. However, changes in area of difference (−23%) and amplitude (−16%) during epinephrine infusion occurred.**

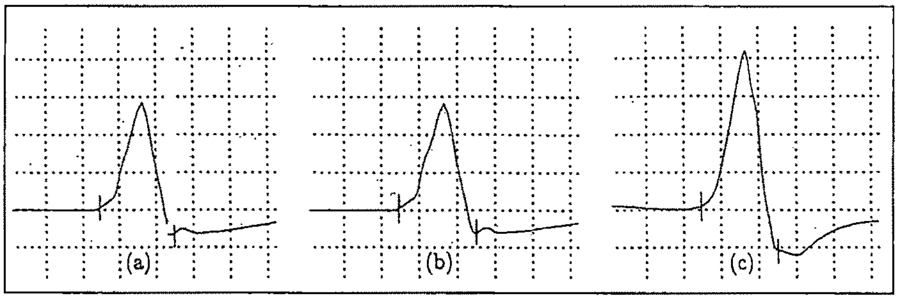

**FIGURE 3. Electrograms from patient 26 during isoproterenol infusion. A signal-averaged intraventricular depolarization is shown from *(a)* passage of sinus rhythm for template construction, *(b)* a subsequent control passage of sinus rhythm, and *(c)* the passage during isoproterenol infusion. The figures are plotted at a paper speed of 200 mm/s with a gain of 75 mV/mm. The 52 ms analysis window of electrogram depolarization is marked on the original 180 ms window. Although no change of correlation coefficient occurred, a large change in area of difference (+33) and amplitude (+56%) during isoproterenol infusion occurred.**

change of area of difference for the 36 patients with stable correlation coefficients during each intervention. Patients with paradoxical changes in correlation coefficient (nos. 13, 32 and 33) were not included in the analysis. For both figures, the data points for pacing at intervals of 600 and 400 ms are not clustered and are too few for linear regression to be appropriate. However, a tighter clustering of data is evident during infusions of epinephrine and isoproterenol, and results of linear regression analysis are included in these diagrams. Whereas changes in amplitude and correlation coefficient were only weakly correlated during both infusion of epinephrine (r = 0.187) and isoproterenol (r = 0.217), the change in amplitude and the change in area of difference were moderately correlated during infusion of epinephrine (r = 0.649) and weakly correlated during infusion of isoproterenol (r = 0.292).

## DISCUSSION

Correlation waveform analysis remains stable during interventional increases in heart rate, whereas the area of difference is less stable and exhibits moderate fluctuations associated with amplitude changes (Figures 1 to 3). Overall waveform morphology remains relatively constant (despite some amplitude variation) during increases in heart rate with or without concurrent changes in sympathetic tone. Therefore, it may be anticipated that a sophisticated scheme of pattern recognition, using a template-based system of arrhythmia identification and regular updating of the sinus rhythm

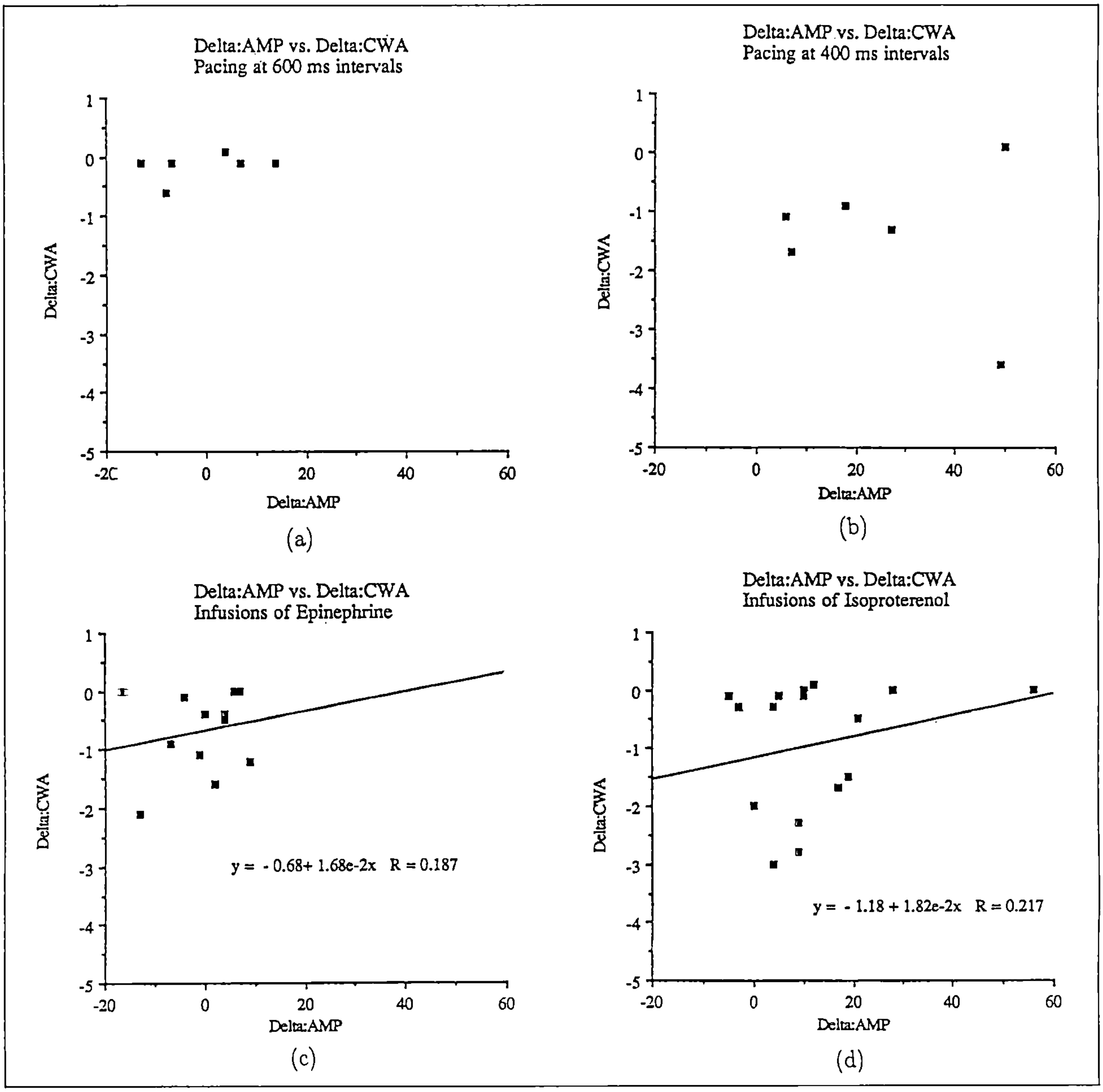

**FIGURE 4. Scatter diagrams of the change in amplitude (Delta:AMP) versus the change of correlation coefficient (Delta:CWA) during *(a)* atrial overdrive pacing at a cycle length of 600 ms, *(b)* pacing at a cycle length of 400 ms, *(c)* epinephrine infusion, and *(d)* isoproterenol infusion. Panels *(c)* and *(d)* include linear regression analysis.**

template, should not be confounded by increases in heart rate during sinus rhythm.

Results of 3 patients undergoing pharmacologic intervention, 1 during epinephrine (no 13) and 2 during isoproterenol (nos. 32 and 33) administration, were widely divergent from most patients evaluated in this study. The morphologic changes noted in these patients, as assessed by the 12-lead electrocardiogram, were not due to paroxysmal development of an intraventricular conduction delay (such as bundle branch block) during drug infusions. Because passive intracardiac electrode leads were used, and because baseline sinus rhythm passages after excretion of exogenously administered drugs were not reconfirmed for stability of electrode location, catheter movement cannot be excluded as a potential cause of the observed changes. For these reasons, we purposely excluded these 3 patients from our statistical analysis and conclusions because of the ambiguity they posed.

**Correlation waveform analysis:** Although this study indicated that correlation waveform analysis remains stable in the presence of accelerated heart rate, other investigators have shown contradictory results. Paul et al[18] demonstrated large changes in electrogram morphology using correlation waveform analysis in a small number of patients during changes in body position. As in the current study, Paul also used a passive electrode catheter, and although data were obtained immediately after exercise, electrograms were not recorded after complete recovery to confirm whether a close correla-

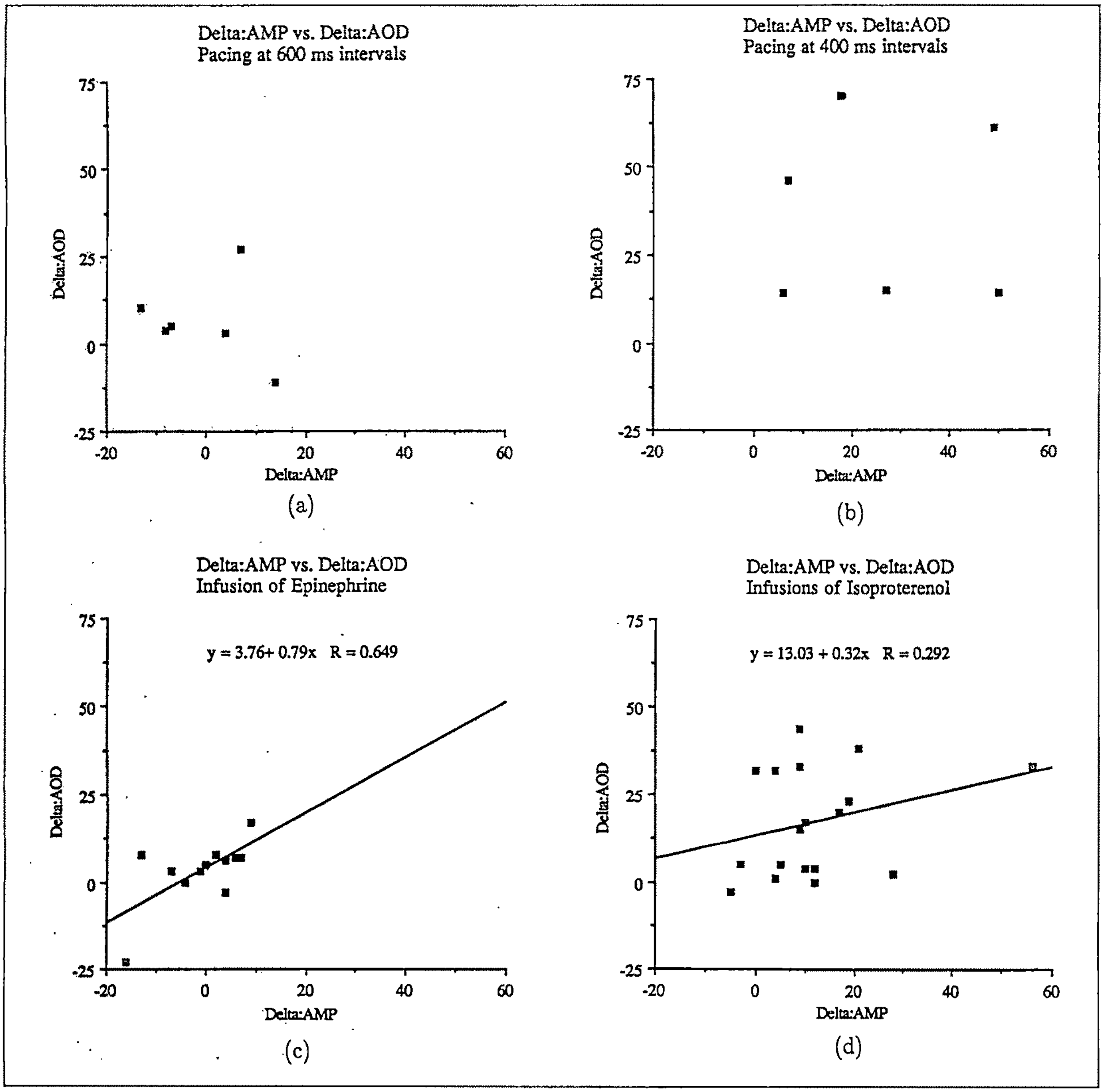

**FIGURE 5. Scatter diagrams of the change in amplitude (Delta:AMP) versus the change in area of difference (Delta:AOD) during *(a)* atrial overdrive pacing at a cycle length of 600 ms, *(b)* pacing at a cycle length of 400 ms, *(c)* epinephrine infusion, and *(d)* isoproterenol infusion. *Panels (c)* and *(d)* include linear regression analysis.**

tion with the original sinus rhythm template remained. Therefore, as with the 3 patients in the current study, catheter migration cannot be excluded as a cause for their observed results.

**Area of difference analysis:** In the present study moderate fluctuations in area of difference that occurred with interventional increases in heart rate were noted. They may not necessarily prove troublesome to template-matching schemes, because the range of area of difference values obtained during accelerated heart rate passages is similar to that previously reported for sinus rhythm at rest.[10,15] The findings of this study therefore suggest that accelerated heart rate may not confound the ability of this technique of analysis to differentiate ventricular tachycardia from sinus rhythm.

**Amplitude analysis:** Although changes in amplitude due to increased heart rate have been demonstrated in previous studies,[19,24,25] controversy exists concerning the value of electrogram amplitude in detecting diverse dysrhythmias.[10,11,26-28] The present study measured peak-to-peak amplitude changes on raw, unfiltered data. The observed effects of atrial overdrive pacing at fast cycle lengths and of isoproterenol administration on electrogram amplitude in the present study are compatible with those of Rosenheck et al.[19] However, they reported amplitude increases during atrial overdrive pacing at 400 ms intervals and during $\beta$ agonism caused by isoproterenol administration as seen on a high-pass filtered version of the signal. As a result, their study consisted of analysis of the derivative of the intracardiac signal, rather than the signal itself.

Studies to date concerning time-domain analysis of intracardiac electrograms have been hampered by experimental limitations such as passive electrode leads, lack of confirmation of electrode migration, and use of artificial intervention to simulate physiologic changes in heart rate. Despite these limitations, the importances of the present study are twofold: (1) Amplitude changes, as seen in the presence of accelerated heart rate, are not necessarily accompanied by significant changes in electrogram morphology as assessed by correlation waveform or area of difference analyses. (2) Electrogram morphologic analysis for the discrimination of ventricular tachycardia from sinus rhythm should remain robust in the face of physiologically accelerated heart rate.

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# Role of Concealed and Supernormal Conductions During Atrial Fibrillation in the Preexcitation Syndrome

Peng-Sheng Chen, MD, and Eric N. Prystowsky, MD

**The hypothesis that retrograde concealed and anterograde supernormal conductions over the accessory pathway are determinants of anterograde accessory pathway conduction during atrial fibrillation (AF) was prospectively tested. For 17 patients during AF, 90 ± 13 (mean ± standard deviation) consecutive beats were analyzed for morphology and VV interval preceding each QRS complex. In 15 patients with both preexcited and normal QRS complexes, after normal complexes, the cycle length preceding the first preexcited QRS complex was 389 ± 69 ms, which was longer than the average cycle length of consecutive preexcited complexes (325 ± 55 ms; p = 0.001). The mean difference was 61 ± 53 ms. After preexcited QRS complexes, the cycle length preceding the first normal QRS complex averaged 423 ± 65 ms, which was significantly longer than the average cycle length of 345 ± 47 ms between consecutively conducted normal QRS complexes (p <0.001). The mean difference was 86 ± 45 ms. These findings suggest retrograde concealed conduction of normally conducted QRS complexes to the accessory pathway can affect anterograde conduction over the accessory pathway, and vice versa. In 2 patients with multiple accessory pathways, 1 accessory pathway conducted only after short preceding cycle lengths (355 to 360 and 181 to 185 ms), which was consistent with supernormal conduction. In conclusion, retrograde concealed conduction to the accessory pathway and anterograde supernormal accessory pathway conduction are factors that, in part, determine accessory pathway conduction during AF.**

**(Am J Cardiol 1991;68:1329–1334)**

There are ≥4 factors that may affect accessory pathway conduction during atrial fibrillation (AF): accessory pathway refractoriness[1]; concealed conduction[2–4]; supernormal conduction[5,6]; and irregularity of the atrial input to the accessory pathway.[7] The ability of concealed and supernormal conductions to influence anterograde conduction over the accessory pathway during AF has not been studied in detail. Evidence to support a role for concealed conduction is the occurrence of consecutive runs of normal QRS complexes interspersed between runs of preexcited QRS complexes.[2] One could postulate that repetitive retrograde conduction into the normal atrioventricular (AV) conduction system after activation of the ventricle over the accessory pathway could yield a series of preexcited QRS complexes, and a run of normal QRS complexes could occur along with retrograde concealment in the accessory pathway after activation of the ventricle over the normal conducting system. If this is true, then the ventricular cycle length at the transition from the first to the second QRS morphology should be longer than the average ventricular cycle length of the second QRS morphology to allow time to recover from the effects of concealed conduction. Regarding supernormality, if an accessory pathway conducts only during the supernormal period, then the preceding cycle length closed by the appearance of this accessory pathway should be confined to a "phase" of supernormality,[5,6] rather than varying according to the atrial input. To test these hypotheses, we prospectively analyzed the morphology and preceding cycle lengths of each QRS complex during AF in 17 patients with preexcitation syndrome who had AF induced during electrophysiologic study. We found data to support concealed and supernormal conductions as important factors in accessory pathway conduction during AF.

## METHODS

Patients with preexcitation syndrome undergoing electrophysiologic study at our institution between May 1987 and May 1988 were prospectively investigated. In all, 17 patients fulfilled the following entrance criteria and were included in the study: (1) AF lasted long enough to have ≥60 QRS complexes available for analysis; and (2) intraoperative epicardial or endocardi-

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From the Division of Cardiology, Department of Medicine, Duke University Medical Center, Durham, North Carolina. This study was performed during the tenure of Clinician Scientist Award 88-414 from the American Heart Association to Dr. Chen. Manuscript received June 7, 1991; revised manuscript received and accepted July 12, 1991.

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**TABLE I** Patient Characteristics

| | No. of Accessory Pathways | |
|---|---|---|
| | 1 | 2 |
| No. of pts. | 9 | 8 |
| Men/women | 6/3 | 6/2 |
| History of syncope | 3 | 4 |
| Clinical atrial fibrillation | 3 | 3 |
| Shortest preexcited RR interval (ms) | 201 ± 25 (158–234) | 208 ± 24 (167–240) |
| Accessory pathway ERP | 249 ± 28 (215–290)* | 250 ± 20 (220–280) |
| Total complexes analyzed | 821 (average 91 ± 11) | 706 (average 88 ± 15) |
| Narrow QRS | 103 (12.5%) | 59 (8.4%) |
| Wide QRS | | |
| Preexcited by dominant AP | 718 (87.5%) | 592 (83.8%) |
| Preexcited by other AP | 0 (0%) | 55 (7.8%) |

*Not obtained in 1 patient owing to recurrent atrial fibrillation during the study.
AP = accessory pathway; ERP = effective refractory period.

al mapping studies, or both, to confirm the location of the accessory pathway(s).

**Electrophysiologic evaluation:** Written and informed consent was obtained before each study. The methods of study of patients with preexcitation syndrome at our institution have been previously described in detail.[8] In brief, patients were studied in the postabsorptive, nonsedated state, and all antiarrhythmic medications were discontinued for ≥5 drug half-lives. Five surface electrocardiographic (I, II, III, $V_1$ and $V_6$) and 9 intracardiac leads were routinely recorded. Refractory periods and conduction characteristics of the AV node and the accessory pathway(s), as well as atria and ventricle, were obtained, and atrial mapping to locate the site of the accessory pathway was performed during reentrant tachycardia and right ventricular pacing. AF was induced by rapid atrial pacing if it did not occur spontaneously during the course of the study. Data were simultaneously recorded on a TEAC XR-510 cassette data recorder and written at 100 mm/sec using a Gould ES-1000 16 channel recorder.

**Data analysis:** After the study, the data were examined to select a period during AF that had the most variations of QRS morphologies. Consecutive intervals were then measured between the ventricular activations recorded by the right ventricular catheter. We chose to measure the VV rather than RR interval, because the beginning of the QRS complex may be indistinct and the peak of the QRS complex may vary during AF, especially in patients with multiple accessory pathways. For each patient, the maximums, minimums, means and standard deviations of the VV intervals between the transitions from normal to preexcited QRS complexes and from preexcited to normal QRS complexes, and between consecutive normally conducted QRS complexes and between consecutive preexcited QRS complexes were obtained. *T* tests were used to compare the differences between the means.[9]

## RESULTS

There were 17 patients (12 men and 5 women) included in the study. An average of 90 ± 13 (mean ± standard deviation) QRS complexes were analyzed for each patient. Among the beats analyzed, 11% were nonpreexcited and 89% were preexcited complexes. Multiple accessory pathways were present in 8 patients. The other 9 patients had 1 accessory pathway, and none of these 9 had multiple wide QRS complex morphologies during AF. Characteristics of the patients are listed in Table I.

**Analysis of concealed conduction:** Data that support the presence of concealed retrograde conduction came from analysis of the results of the preceding cycle length and its relation to the anterograde QRS morphology in 15 patients with both normal and preexcited QRS complexes during AF. In patients with >1 preexcited QRS morphology, only the dominant morphology was included. Figure 1 demonstrates these measurements during AF in a patient with a posteroseptal accessory pathway. The wide QRS complexes (initial and last 3 beats) are preexcited. The narrow QRS complexes (middle 8 beats) are not preexcited. The numbers below the QRS complexes represent the intervals between consecutive right ventricular activations. The preceding cycle length of beat no. 2 is 220 ms, that of beat no. 3 is 190 ms, and so forth. Note that the VV intervals during the transitions from the preexcited to the normal complex and from the normal to the preexcited complex were longer than other VV intervals on the same tracing.

Fifteen patients with both normal and preexcited QRS complexes present during AF were included for analysis (Table II). Two patients were not included because 1 of the pathways conducted only during the supernormal period. A total of 56 episodes were observed when nonpreexcited preceded preexcited QRS complexes, and 48 were identified when preexcited preceded nonpreexcited complexes. The interval between the transition from normal to preexcited QRS complexes averaged 389 ± 69 ms, which was significantly longer than the average cycle length of 325 ± 55 ms between consecutive preexcited QRS complexes in the same episodes. Mean difference was 61 ± 53 ms. However, these results did not imply that the VV intervals at transition were always longer than the maximal consecutively preexcited VV intervals. On the contrary, in 13 of 15 tracings ≥1 consecutively preexcited VV interval was longer than the minimal VV interval observed at the transition from normal to preexcited complex in the same tracing.

In 3 of 15 tracings, only 1 normally conducted beat was seen; therefore, measuring the VV interval between normally conducted beats was not possible. In the remaining 12 tracings, the cycle lengths at transition from the preexcited to normal complex averaged 423 ± 65 ms, which was significantly longer than the average cycle length of 345 ± 47 ms between consecutive normally conducted complexes (Table II). Mean difference was 86 ± 45 ms. In 8 of 12 tracings, $\geq 1$ consecutive normally conducted VV interval was longer than the minimal VV interval observed at the transition from preexcited to normal complex in the same tracing.

Despite the statistically significant differences between the preceding VV intervals at the transition from normal to preexcited complexes and those of preexcited complexes, exceptions were found in patients 4 and 12 (Table II). In these 2 patients, we found a shorter preceding cycle length at the transition from normal to preexcited QRS complexes than the average preceding cycle length of all preexcited complexes. Patient 4 had an intermediate septal pathway[10] close to the AV node. Patient 12 had a posteroseptal pathway. The reason for these atypical findings is unknown.

**TABLE II** Preceding Cycle Lengths at Transition Between Preexcited and Nonpreexcited Complexes

| | Average | | | | |
|---|---|---|---|---|---|
| Patient No. | Normal to Preexcited | Preexcited | Preexcited to Normal | Normal | Dominant AP Location |
| 1 | 525 | 439 | 520 | 447 | PS |
| 2 | 332 | 269 | 473 | 325 | RF |
| 3 | 385 | 291 | —* | —* | LF |
| 4 | 305 | 343 | 373 | 345 | IS |
| 5 | 348 | 324 | 329 | 301 | LF |
| 6 | 391 | 241 | —* | —* | LF |
| 7 | 362 | 309 | 362 | 358 | LF |
| 8 | 295 | 261 | 384 | 318 | PS |
| 9 | 470 | 359 | 447 | 333 | RF |
| 10 | 423 | 380 | 383 | 333 | PS |
| 11 | 444 | 377 | 545 | 404 | LF |
| 12 | 347 | 370 | 442 | 375 | PS |
| 13 | 492 | 345 | —* | —* | LF |
| 14 | 392 | 312 | 425 | 337 | PS |
| 15 | 323 | 260 | 391 | 269 | LF |
| Mean ± SD | 389 ± 69 | 325 ± 55† | 423 ± 65 | 345 ± 47‡ | |

*As only 1 normally conducted beat was observed, the average of the normal beats is not available for comparison.

†p <0.001 compared with preceding cycle length at transition from normal to preexcited complex; ‡p <0.001 compared with preceding cycle length at transition from preexcited to normal complex.

AP = accessory pathway; IS = intermediate septal; LF = left free wall; PS = posteroseptal; RF = right free wall; SD = standard deviation

**Evidence that supports supernormal conduction as a determinant factor of accessory pathway conduction:** Supernormal conduction is best defined as propagation of an impulse that occurs at a time when the tissue would be expected to be refractory.[5] We observed this phenomenon during AF in 2 patients. Each of these 2 patients had 2 accessory pathways with 2 morphologies of QRS complexes observed during AF. The dominant QRS morphologies were the ones that were most frequently observed during AF. The nondominant QRS morphologies occurred only with a preceding cycle

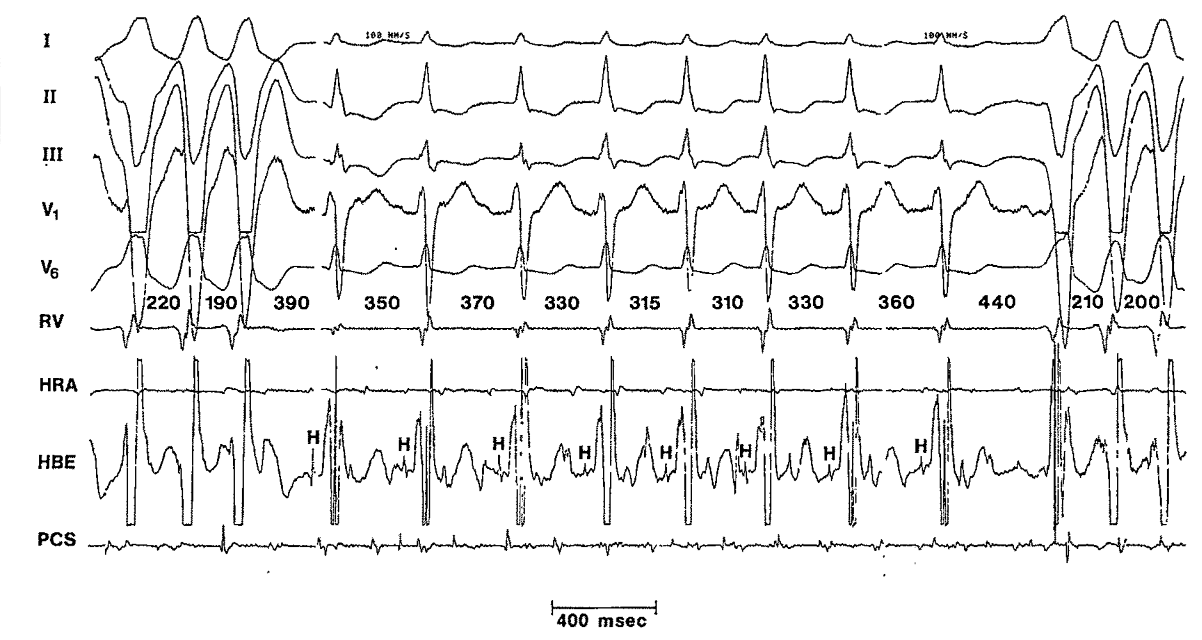

**FIGURE 1. Episode of atrial fibrillation observed in patient with posteroseptal accessory pathway. Surface electrocardiographic leads I, II, III, $V_1$ and $V_6$, and right ventricular (RV), high right atrium (HRA), His bundle (HBE) and proximal coronary sinus (PCS) electrograms were simultaneously recorded. Numbers represent intervals between right ventricular electrograms in ms. See text for details.**

length similar to or less than the shortest QRS complexes of the dominant morphology, and were associated with narrow ranges of preceding VV intervals that varied between 355 and 360 ms in patient 16 (Figure 2), and 181 and 185 ms in patient 17 (Figure 3). This narrow range of VV intervals is compatible with supernormal conduction.[5,6]

## DISCUSSION

**Major findings of the study:** In this study we demonstrated that during AF, the transition from either the normal to preexcited or the preexcited to normal QRS complex was associated with longer VV intervals than the mean VV intervals. Assuming the larger intervals were due solely to retrograde concealment, which of course we can only hypothesize, retrograde concealment prolonged the VV interval by 61 ± 53 ms during the transition from normal to preexcited complexes, and by 86 ± 45 ms during the transition from preexcited to normal complexes. These values represent in part the contribution of retrograde concealment on subsequent AV conduction through the accessory pathway and AV node, respectively. The large standard deviation can be explained by the fact that the effects of retrograde concealment are determined not only by the timing of retrograde activation in the accessory pathway and AV node, but also by the timing of the atrial input in the accessory pathway and AV node. In addition, repetitive anterograde concealment of atrial input to the accessory pathway and AV node may further influence the conduction over these pathways, resulting in large variations of the preceding cycle lengths. Obviously, there are multiple mechanisms that determine whether anterograde conduction will occur over the normal system or accessory pathway, or both, and it is impossible to determine for any given beat the importance of retrograde concealed conduction or other factors that govern which system will be used for ante-

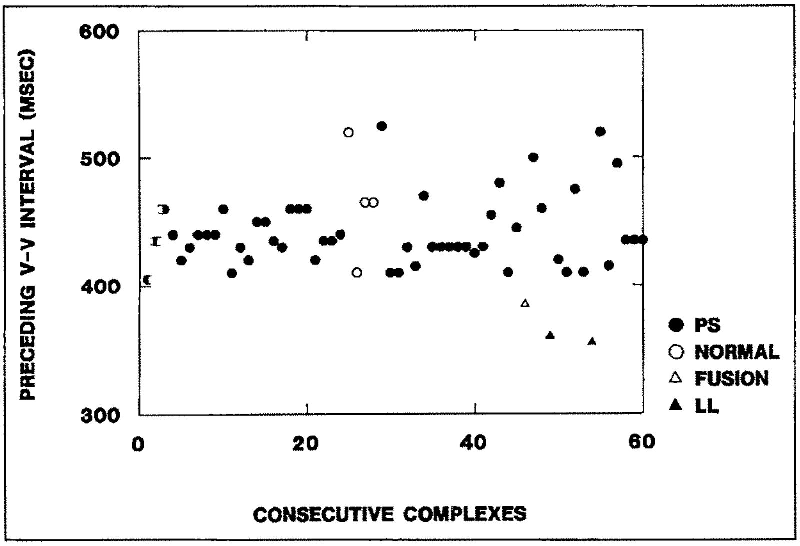

**FIGURE 2. Preceding VV intervals of consecutive QRS complexes during atrial fibrillation in patient 16. Note that at transition of QRS complex morphologies from that associated with posteroseptal accessory pathway to normal QRS complex and from normal QRS complex to that associated with posteroseptal accessory pathway, preceding cycle lengths are longer than average. Shorter than average VV intervals preceding complexes conducted through left lateral accessory pathway are compatible with supernormal conduction. LL = left lateral; PS = posteroseptal.**

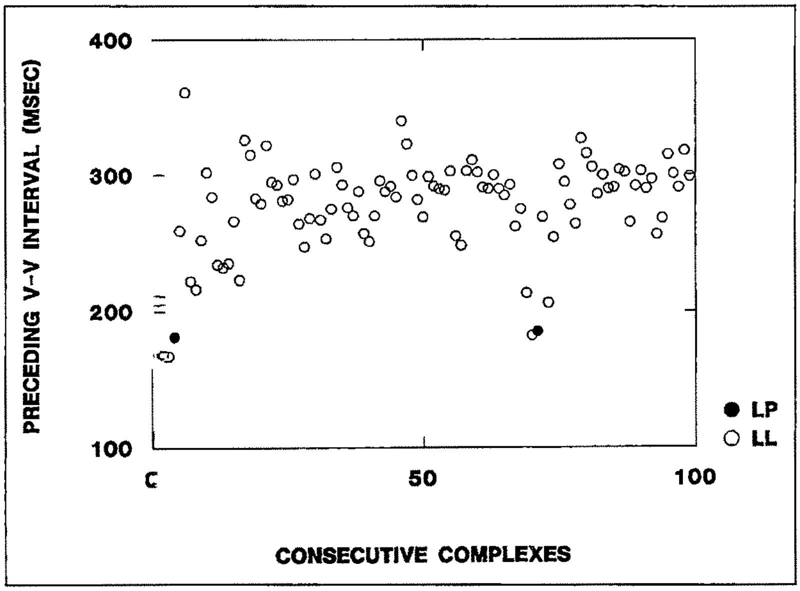

**FIGURE 3. Preceding VV interval of consecutive QRS complexes during atrial fibrillation in patient 17. No normally conducted QRS complexes present. Majority of QRS complexes are compatible with conduction over left lateral free wall accessory pathway. Two QRS complexes had morphology compatible with conduction over left posterior free wall accessory pathway. These QRS complexes were observed only with short preceding cycle lengths, compatible with supernormal conduction. LL = left lateral; LP = left posterior.**

rograde conduction. Because multiple mechanisms are involved in accessory pathway conduction, the transitional VV intervals may not always be longer than the nontransitional VV intervals in individual tracings.

**Atrioventricular conduction during atrial fibrillation:** AF is associated with irregular ventricular responses in patients with and without accessory pathways. The mechanism of the irregularity is not completely understood. If the conduction is purely determined by the refractory periods of the normal system and accessory pathway, then during AF, the ventricles should be activated shortly after each moment at which the respective conduction system becomes excitable. Because the frequency of stimuli applied to the AV node and accessory pathway is high, the cycle length variation should be small. However, this clearly is not what has been observed during AF. Experimental evidence demonstrates that anterograde concealed conduction is also a factor that determines the conduction of the AV node.[11,12] In addition to AV node refractoriness and anterograde concealed conduction, the direction of atrial input to the AV node may also be a factor in determining AV conduction.[13]

The aforementioned studies[11-13] were performed in patients or animals with conduction over the normal AV node-His Purkinje system. In patients with preexcitation syndrome, there is ≥1 accessory pathway present. Thus, in addition to the above factors, an interaction between the normal and abnormal pathways through retrograde concealed conduction may also be a factor that determines the ventricular response during AF. Although there are good data to support the hypothesis that retrograde concealed conduction is demonstrable during regular rhythm,[2-4] there is little evidence to support the claim that this factor is operative during AF. The data presented in this report are important because they lend support to the hypothesis that retrograde concealed conduction is an important factor that determines the anterograde accessory pathway conduction.

**Supernormal conduction:** Supernormal conduction over an accessory pathway is a well-recognized phenomenon.[5,6] In these reports, a "phase" of supernormal conduction was usually present. This phase is defined as a range of $A_1$–$A_2$ intervals resulting in conduction over the accessory pathway inside the refractory period of the latter.[6] In patients with manifest ventricular preexcitation, the supernormal phase can be demonstrated by progressively shortening the $A_1$–$A_2$ interval and observing that the QRS complex after the $A_2$ is preexcited with relatively long $A_1$–$A_2$ intervals and nonpreexcited with shorter intervals when the accessory pathway "effective refractory period" is reached, and that with further shortening of the $A_1$–$A_2$ intervals there is recurrence of ventricular preexcitation.[5] Because supernormality is demonstrable in various excitable tissue,[14-16] one might expect to observe this phenomenon in accessory pathways.

In this study, 2 accessory pathways were found to conduct with short preceding VV intervals. There appeared to be a phase of supernormality of only 4 to 5 ms duration. These findings are compatible with supernormal conduction over the accessory pathway during AF.

**Other possible causes of multiple morphologies observed during atrial fibrillation:** Ventricular premature complexes and aberrant conduction can result in wide QRS complex beats resembling preexcitation. Without direct accessory pathway recordings, it is not possible to rule out this possibility completely. However, there are ≥2 observations that strongly suggest that the different wide complex morphologies in patients 16 and 17 represented conduction over 2 accessory pathways. First, the nondominant wide QRS complex morphology was consistent with a distinctive preexcited morphology.[17] Second, at surgery, a second accessory pathway was identified that was located at the site predicted at electrophysiologic study. Further research of accessory pathway conduction should use computerized mapping techniques to demonstrate ventricular preexcitation over the second accessory pathway and to correlate conduction with preceding cycle lengths and atrial activation proximal to the accessory pathway. These studies should help to identify the mechanisms that govern accessory pathway conduction during AF.

**Study limitation:** One major limitation of this study is that these patients may not be representative of all patients with preexcitation syndrome. These patients were referred to surgery for symptomatic supraventricular arrhythmias and thus represent a highly selected patient cohort. There was a high proportion of multiple pathways. It is thus possible that the results of this study may be biased by the selection process.

**Clinical significance:** The single most important prognostic indicator in patients with preexcitation syndrome is the shortest preexcited RR interval during AF.[18] Because of the imperfect correlation between the shortest preexcited RR interval and the anterograde effective refractory periods of the accessory pathway,[18] factors other than accessory pathway refractoriness probably contribute to conduction over the accessory pathway during AF and therefore alter the potential risk of these patients. In this report, we summarized our observations on accessory pathway conduction during AF in patients with preexcitation syndrome referred for surgical treatment. Although there was a significant correlation between accessory pathway refractoriness and the shortest RR interval during AF,[1] other factors such as retrograde concealment and supernormal conduction are also important in determining accessory pathway conduction. The role of supernormality in uncovering an otherwise undetected accessory pathway is important if operative therapy is contemplated.

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# Superior Vena Cava Flow and Tricuspid Anular Motion After Cardioversion of Atrial Fibrillation, and Role of Right Atrial Relaxation on Systolic Venous Return

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Shigefumi Morioka, MD, and Katsutoshi Moriyama, MD

**To determine whether atrial relaxation or systolic descent of the tricuspid anulus is the predominant factor determining systolic venous return, 22 patients with atrial fibrillation were studied. Venous return (i.e., superior vena cava (SVC) flow) was measured using pulsed Doppler echocardiography. Systolic descent of the tricuspid anulus (i.e., total excursion of tricuspid anulus during systole) was also measured using echocardiography. Serial examinations were performed before and after cardioversion of atrial fibrillation in 15 patients. In 11 patients, both the total excursion of the tricuspid anulus and SVC flow were examined in relation to the ratio of the preceding to the pre-preceding RR interval (R2/R1). Systolic forward flow of SVC increased as the ratio of late diastolic to total excursion of the tricuspid anulus (i.e., right atrial systolic function) increased. It correlated significantly with the ratio of late diastolic to total excursion of the tricuspid anulus but not with total excursion. Total excursion of the tricuspid anulus correlated significantly with R2/R1, but systolic forward flow of SVC did not. These results indicate that atrial relaxation rather than systolic descent of the tricuspid anulus was the predominant factor determining systolic forward flow in the SVC.**

**(Am J Cardiol 1991;68:1335–1339)**

Forward flow through the superior vena cava (SVC) is normally biphasic.[1,2] The first phase occurs during ventricular systole and the second during early diastole. Many investigators have studied the determinants of systolic forward flow of the vena cava.[2–8] It has been reported that systolic descent of the tricuspid anulus or atrial relaxation, or both, can be major determinants of forward flow of the vena cava during systole. The role of systolic descent of the tricuspid anulus on venous return has been emphasized by several investigators,[3–6] whereas others have emphasized the role of atrial relaxation.[2,7,8] Thus, the issue of which event is the predominant factor determining systolic forward flow of venous return remains controversial. Atrial activity is absent in atrial fibrillation (AF), and although normal atrial electrical activities return immediately after successful cardioversion, effective atrial contraction may be absent or reduced for days after cardioversion.[9–12] The present study is designed to evaluate the relation between tricuspid anular motion and SVC flow before and after cardioversion of AF, and to determine whether systolic descent of tricuspid annular motion or atrial relaxation is the major determinant of systolic venous return.

## METHODS

The study consisted of 22 consecutive patients (15 men and 7 women, age range 23 to 84 years [average 63]) with AF. Sixteen patients had lone AF, and 6 had underlying heart disease, including mitral (3 patients) and aortic (2) valvular diseases, and coronary artery disease (1). Two patients had slight dilatation of the left ventricle, but none had right ventricular hypertrophy, dilatation of the right ventricle, or significant tricuspid regurgitation. The duration of AF before cardioversion ranged from 1 day to 16 months (average 3 months). Nineteen age-matched subjects (11 men and 8 women; age range 30 to 79 years [average 58]) with normal sinus rhythm, no history of heart disease, and no abnormalities of the heart by 2-dimensional echocardiography served as control subjects.

Fifteen patients with AF underwent direct-current cardioversion or cardioversion by drugs. Synchronized

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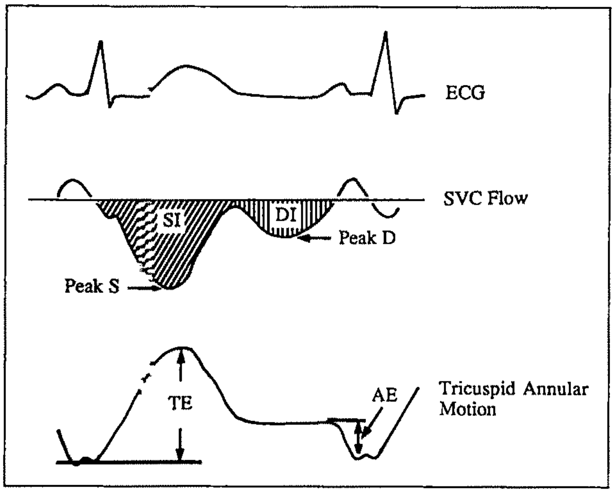

**FIGURE 1. Schematic diagram of superior vena cava (SVC) flow and tricuspid anular motion. AE = late diastolic excursion of the tricuspid annulus due to atrial contraction; DI = time velocity integral of the diastolic wave; ECG = electrocardiogram; Peak D = peak velocity of the diastolic wave; Peak S = peak velocity of the systolic wave; SI = time velocity integral of the systolic wave; TE = total excursion of the tricuspid anulus.**

shocks of 60 to 150 J successfully reverted AF to sinus rhythm. Doppler and M-mode echocardiography were performed before and 1 hour, 6 hours, 24 hours, 2 days, 3 days and 1 week after cardioversion. The strength of ventricular contractions varies in the presence of AF owing to relative changes in cycle length (i.e., the ratio of the preceding RR interval [R2] to the pre-preceding RR interval [R1]).[13,14] In 11 patients with AF, including 4 who underwent cardioversion, we examined the relation between total excursion of the tricuspid anulus during ventricular contraction and the R2/R1 ratio, as well as that between SVC flow pattern and the R2/R1 ratio.

The equipment used was a real-time 2-dimensional Doppler flow imaging system (Toshiba SSH 65A) combined with a 2.5 and 3.5 MHz transducer. Doppler echocardiograms were recorded in the SVC and in the inflow tract of the right ventricle. SVC flow was recorded from the supraclavicular approach, with subjects in the supine position. The sampling volume was

**TABLE I** Doppler and Echocardiographic Parameters

| | | After Cardioversion | | | |
|---|---|---|---|---|---|
| | AF | 1 Hour | 2 Days | 1 Week | Control Subjects |
| Superior vena cava flow | | | | | |
| Peak systolic velocity (cm/sec) | 12.3 ± 5.1* | 21.6 ± 6.4*† | 31.6 ± 9.2*‡§ | 34.9 ± 11.9‡§ | 37.8 ± 5.5 |
| Peak diastolic velocity (cm/sec) | 26.6 ± 9.7* | 20.8 ± 9.5 | 22.1 ± 7.6 | 22.1 ± 11.4 | 18.5 ± 6.4 |
| Ratio of systolic to diastolic velocities | 0.5 ± 0.1* | 1.2 ± 0.6*‡ | 1.6 ± 0.7*‡ | 1.7 ± 0.4*‡ | 2.3 ± 0.8 |
| Time-velocity integral of systolic wave (cm) | 2.0 ± 0.8* | 5.0 ± 1.8*‡ | 7.1 ± 2.2*‖‡ | 8.6 ± 2.4‡§ | 8.7 ± 1.7 |
| Time-velocity integral of diastolic wave (cm) | 6.1 ± 2.6* | 4.2 ± 2.2 | 4.6 ± 2.2 | 5.1 ± 2.6 | 3.5 ± 1.8 |
| Ratio of systolic to diastolic integral | 0.4 ± 0.1* | 1.6 ± 1.1* | 2.2 ± 2.6*‡ | 1.9 ± 0.7¶ | 3.0 ± 1.3 |
| Tricuspid anular motion | | | | | |
| Total excursion | 12.7 ± 3.8* | 14.4 ± 3.2* | 17.1 ± 3.4‡¶ | 17.5 ± 2.9† | 19.6 ± 4.2 |
| Late diastolic excursion | — | 3.4 ± 1.7* | 5.3 ± 2.2* | 6.8 ± 2.0§ | 8.3 ± 2.1 |
| Ratio of late diastolic to total excursion (%) | — | 23.7 ± 9.3* | 30.3 ± 8.5* | 31.2 ± 8.1§ | 42.4 ± 6.9 |
| Tricuspid flow | | | | | |
| Ratio of early to late diastolic velocities | — | 0.7 ± 0.3¶ | 0.7 ± 0.2¶ | 0.9 ± 0.3§ | 0.9 ± 0.2 |

*$p < 0.01$ vs control data; †$p < 0.05$ vs AF; ‡$p < 0.01$ vs AF; §$p < 0.01$ vs 1 hour after cardioversion; ‖$p < 0.05$ vs 1 hour after cardioversion; ¶$p < 0.05$ vs control data.
AF = atrial fibrillation.

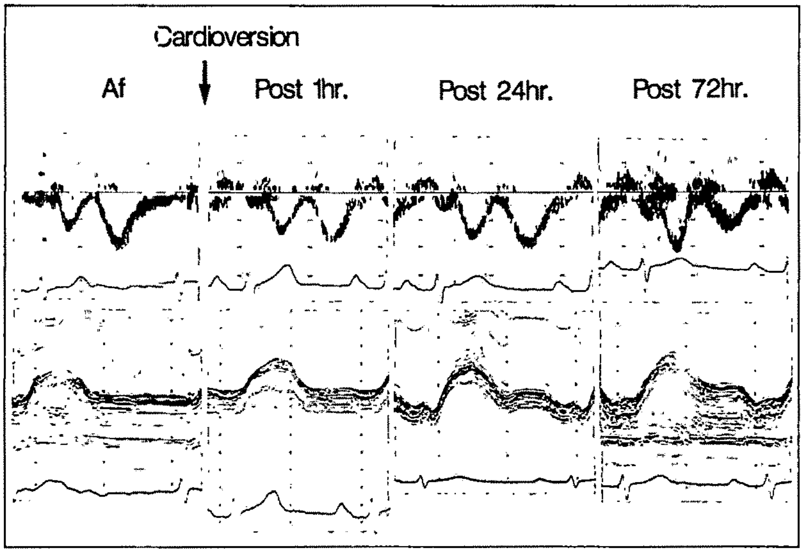

**FIGURE 2. Serial superior vena cava flow velocity profiles *(top)* and echocardiograms of tricuspid anular motion *(bottom)* from 1 patient. Note progressive increase in both peak systolic velocity of superior vena cava flow and late diastolic excursion of tricuspid anulus due to atrial contraction. Af = atrial fibrillation.**

positioned at the center of the SVC approximately 5 cm under the transducer. Tricuspid flow was recorded with subjects in the left semilateral position. The sampling volume was positioned at the center of the tricuspid anulus in a 4-chamber view. M-mode echocardiograms were recorded with subjects in the semilateral position. Motion of the tricuspid anulus during 1 cardiac cycle was recorded with the M-mode cursor directed from the apical 4-chamber view. Doppler and M-mode echocardiograms were recorded on a strip chart recorder at a paper speed of 50 mm/sec during held expiration.

The following parameters were measured from the waveform of SVC flow: (1) peak velocity of systolic and diastolic waves; (2) systolic-to-diastolic peak velocity ratio; (3) time-velocity integral of systolic and diastolic waves; and (4) systolic-to-diastolic time-velocity integral ratio (Figure 1). Late-to-early filling velocity ratio was measured from the waveform of ventricular filling. The following parameters were measured from the M-mode echocardiogram: (1) total excursion toward the apex of the tricuspid anulus during ventricular contraction; (2) late diastolic excursion of the tricuspid anulus during atrial contraction; and (3) ratio of late diastolic to total excursion of the tricuspid anulus. The values obtained over 3 to 5 beats were averaged.

Values are expressed as mean ± standard deviation. A p value <0.05 was considered statistically significant. Echocardiographic variables were evaluated by least-square linear regression analysis.

## RESULTS

**Superior vena cava and tricuspid flows, and tricuspid anular motion before and after cardioversion (Table I):** In all patients with AF, the systolic wave of SVC flow was smaller than the diastolic wave. In all patients who underwent cardioversion, peak systolic velocity of SVC flow gradually increased and peak diastolic velocity gradually decreased by the seventh day after cardioversion (Figure 2 and Table I). Consequently, the ratio of systolic to diastolic peak velocities increased (0.5 ± 0.1 to 1.2 ± 0.6) one hour after cardioversion, and then gradually increased to 1.7 ± 0.4 by the seventh day. The ratio of systolic to diastolic time-velocity integrals changed after cardioversion in the same way as the ratio of systolic to diastolic peak velocities.

The ratio of late to early filling velocities of tricuspid flow was smaller in patients with AF than in control subjects at both 1 hour and 2 days after cardioversion, but was not significantly different by the 7th day.

The total excursion of the tricuspid anulus before cardioversion was significantly smaller in patients with

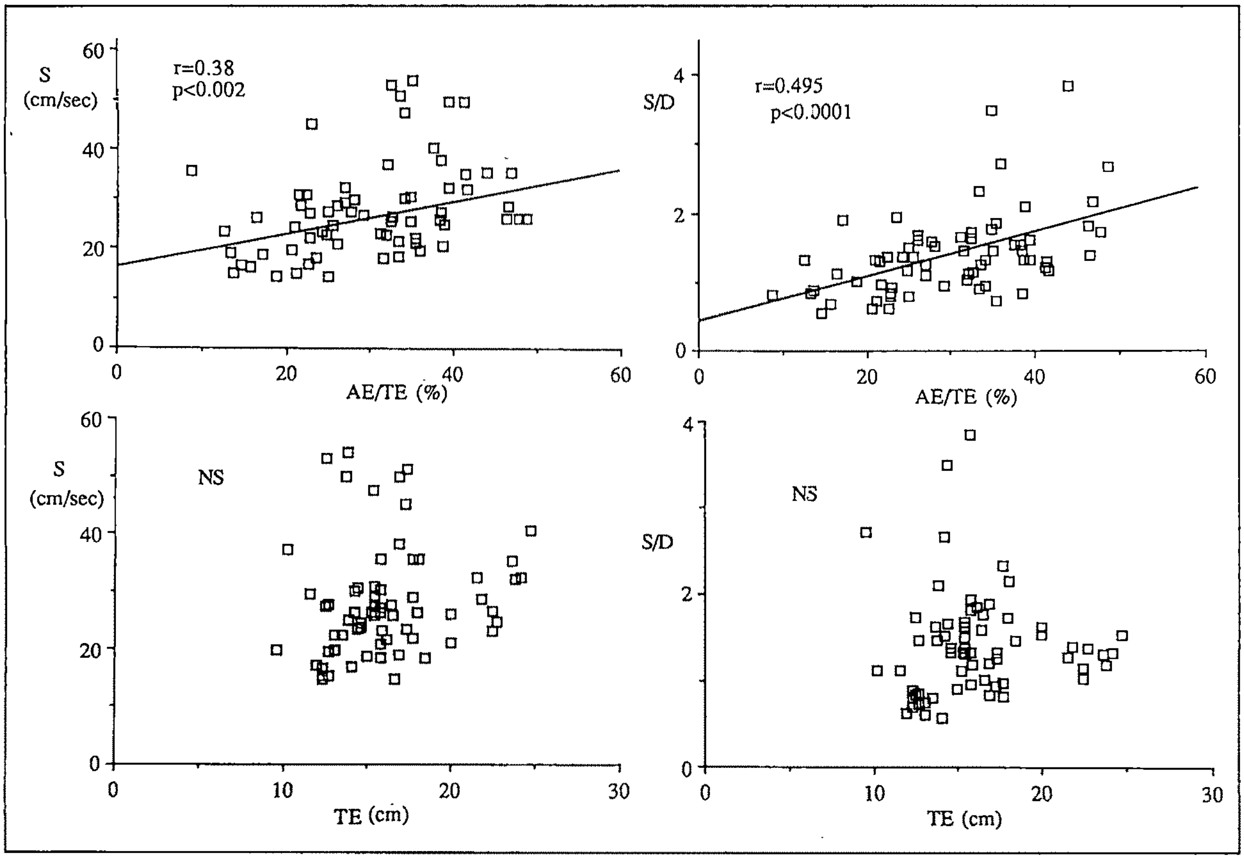

**FIGURE 3.** ***Top,*** **relations between peak systolic (S) velocity in superior vena cava and excursion after atrial contraction to total excursion (AE/TE) of tricuspid anulus** ***(top left),*** **and between ratio of systolic to diastolic (S/D) peak velocities of superior vena cava flow and AE/TE** ***(top right).*** **Bottom, relations between S and TE** ***(bottom left),*** **and between S/D and TE** ***(top right).***

AF than in control subjects. The ratio of late diastolic to total excursion of the tricuspid anulus increased relatively gradually after cardioversion (Figure 2 and Table I).

**Relation between Doppler and echocardiographic parameters:** In all data before and after cardioversion of AF in 15 patients, the ratio of late diastolic to total excursion of the tricuspid anulus correlated positively with the ratio of systolic to diastolic peak velocities of SVC flow (r = 0.50, p <0.0001), and with peak systolic velocity of SVC flow (r = 0.38, p <0.002) (Figure 3, top). It also correlated positively with the ratio of systolic to diastolic time-velocity integrals of SVC flow (r = 0.40, p <0.005), and with the time-velocity integral of the systolic wave (r = 0.48, p <0.0001). The late diastolic to total excursion ratio did not correlate significantly with peak diastolic velocity of SVC flow or with the time-velocity integral of the diastolic wave.

The ratio of late to early filling velocities of tricuspid flow correlated significantly with both the ratio of systolic to diastolic peak velocities (r = 0.61, p <0.0001) and the ratio of systolic to diastolic time-velocity integrals of SVC flow (r = 0.56, p <0.0001). The late-to-early velocity ratio of tricuspid flow did not correlate significantly with peak systolic velocity, but did with the time-velocity integral of the systolic wave (r = 0.31, p <0.05).

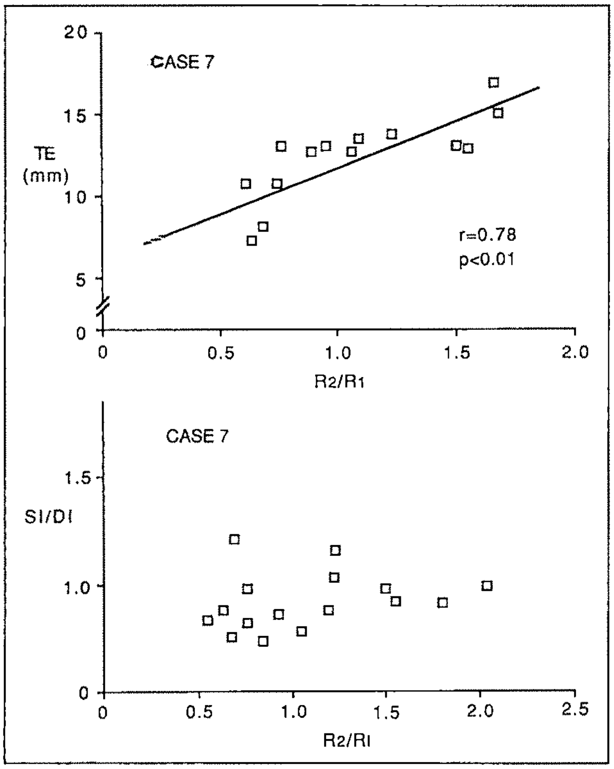

**FIGURE 4. Case 7.** ***Top,*** **Relation between total excursion (TE) of tricuspid anulus and ratio of preceding to pre-preceding RR intervals (R2/R1). A good correlation is seen.** ***Bottom,*** **relation between ratio of systolic to diastolic time-velocity integrals (SI/DI) of superior vena cava flow. No correlation is seen.**

In all data before and after cardioversion of AF in 15 patients, the total excursion of the tricuspid anulus did not correlate significantly with the ratio of systolic to diastolic peak velocities or with peak systolic velocity (Figure 3, bottom). In 11 patients with AF, the R2/R1 ratio correlated significantly with total excursion, but not with the ratio of systolic to diastolic time-velocity integrals or the time-velocity integral of the systolic wave (Figure 4).

## DISCUSSION

Some investigators have reported that effective atrial contraction may be absent or weak for days or weeks after cardioversion of AF to sinus rhythm.[9-12] Recently, serial evaluations of atrial function by Doppler echocardiography before and after cardioversion of AF have been reported.[11,12] Manning et al[11] showed that peak atrial filling wave velocity of mitral valve flow continued to increase up to 12 to 22 days after cardioversion. Dethy et al[12] reported that the percent increase of atrial filling wave velocity of mitral valve flow between 4 and 24 hours after cardioversion is an excellent predictor of maintained sinus rhythm. In the present study, we serially recorded tricuspid anular motion before and after cardioversion of AF to evaluate right atrial mechanical function. We found, as did the previous reports, that atrial contraction, as measured by late diastolic excursion or late diastolic to total excursion ratio, slowly improved between 1 hour and 7 days after successful cardioversion.

Forward flow through the SVC is normally biphasic. Systolic forward flow through the SVC may be influenced by right atrial relaxation or systolic descent of the tricuspid anulus, or both. Sivaciyan and Ranganathan[3] reported that patients with AF had abnormal forward flow patterns in the jugular veins, systolic being less than diastolic forward flow. They suggested that the abnormal flow pattern was related to decreased right heart function, which in turn diminished systolic descent of the tricuspid anulus rather than the arrhythmia itself. Keren et al[15] observed that disturbances of the pulmonary venous flow were immediately reversed after cardioversion of AF to sinus rhythm, or after atrioventricular sequential pacing in complete atrioventricular block. They concluded that both atrial and ventricular contraction and relaxation were important determinants of pulmonary venous flow. The extent to which systolic descent of the mitral anulus contributed to pulmonary venous flow was unclear, because these authors did not study mitral anular motion. More recently, Keren et al[16] studied the relation between pulmonary venous flow pattern and mitral annular motion in normal subjects and in patients with dilated cardiomyopathy. The abnormal patterns of pulmonary venous flow were associated with either absence of mitral anular motion, AF or significant mitral regurgitation. However, patients in sinus rhythm having decreased motion of the mitral anulus had normal biphasic patterns. In the present study, we observed that neither the ratio of systolic to diastolic peak velocities nor peak systolic velocity of SVC flow correlated with total excursion (i.e., systolic descent of the tricuspid anulus). R2/R1 ratio, a predictor of contractility in AF,[13,14] correlated significantly with total excursion, reflecting right ventricular contraction. However, R2/R1 ratio did not correlate significantly with the ratio of systolic to diastolic time-velocity integrals and with the time-velocity integral of the systolic wave. These results indicate that systolic descent of the atrioventricular ring itself is not a major determinant of systolic forward flow of SVC.

Since this study included mainly lone AF, our observations may not apply to patients with various heart diseases. Further study is needed in subgroups of patients with various heart diseases.

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# Operative Mortality with Implantation of the Automatic Cardioverter-Defibrillator

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**Operative mortality was studied in 939 consecutive patients undergoing initial implantation of an automatic implantable cardioverter-defibrillator (AICD™) at 15 hospitals. Twenty-nine (3.1%) patients died during the first 30 days after surgery. Among patients who survived beyond the first 30 postoperative days, ejection fraction data were available in 219; compared with the mortality group, these survivors had a significantly higher ejection fraction (34 ± 15 vs 26 ± 10%, respectively, p <0.001), despite similar age, sex, underlying heart disease, type of presenting arrhythmia and prevalence of concomitant surgery. The causes of perioperative death were sudden in 7 (24%), tachyarrhythmic/nonsudden in 5 (17%), cardiac nonarrhythmic in 9 (31%), and noncardiac in 8 (28%). Twenty-four (83%) of the deaths occurred before hospital discharge, and in all 9 instances of in-hospital sudden and tachyarrhythmic/nonsudden death, the initial recorded rhythm was sustained ventricular tachycardia or fibrillation; in 5 (56%) of these 9 patients the AICD had been in a deactivated state since implantation. Other possible contributory factors in the 12 sudden or tachyarrhythmic/nonsudden deaths included acute myocardial ischemia or infarction in 2 (17%), and "device proarrhythmia" in 3 (25%) that were AICD-related in 2 and secondary to an antitachycardia pacemaker in another; defibrillation threshold testing was not performed in 3 patients (1 of whom had terminal ventricular fibrillation).**

**Thus, in this multicenter experience with thoracotomy requiring AICD implantation, operative (30-day) mortality was 3.1% and correlated inversely with left ventricular ejection fraction. Further studies are needed to explore the potential role of management practices in the occurrence of sudden or tachyarrhythmic/nonsudden death, which accounted for 41% of all postoperative fatalities in this AICD implantation series.**

**(Am J Cardiol 1991;68:1340–1345)**

The automatic implantable cardioverter-defibrillator (AICD™) is now recognized as a valuable therapeutic method for preventing sudden death in patients at high risk for recurrent, sustained, life-threatening ventricular tachyarrhythmias.[1] As indications for device therapy expand, risk-benefit considerations are being given greater attention. One important factor in such assessments is the death rate that may be expected to result either directly or indirectly from the implantation process itself. To estimate this risk and characterize operative mortality in a large patient population, we undertook a retrospective, multicenter study of early fatality after implantation of the AICD, with special emphasis on perioperative sudden and tachyarrhythmic/nonsudden death.

## METHODS

All patients undergoing first-time implantation with the AICD model 1400 and 1500 series (Cardiac Pacemakers, Inc., St. Paul, Minnesota) at 13 medical centers (total of 15 hospitals/institutions; see Appendix) from July 1, 1982 through July 10, 1988, were enrolled in the total study cohort. Follow-up data were collected until August 10, 1988. The patient implant list was derived from a registry maintained by Cardiac Pacemakers, Inc., and consisted of 939 patients. AICD model 1400 series (1400, 1410 and 1420) were implanted in 476 patients (51%), and model 1500 Series (1500, 1510 and 1520) in the remaining 463 (49%).

Information on surgical approaches and lead configurations used during the study period was obtained by surveying investigators regarding implantation practices at each center. Among the 15 participating hospitals, the lateral thoracotomy approach was used predominantly in 10 (67%), whereas the median sternotomy approach was preferred in 4 (27%) and the subcostal approach in 1 (7%). The "patch-patch" lead was the predominant configuration in 13 hospitals (87%)

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whereas the "spring-patch" configuration was preferred in 2 (13%).

**Group designations:** All patients who died within the first 30 days after their initial AICD implantation formed the mortality group. Among the 910 implantees who survived their first 30 days, left ventricular ejection fraction values were available in 219 (through the Cardiac Pacemakers, Inc. registry), and these patients formed the reference group of the study. Comparisons between the 2 groups were obtained on clinical descriptors provided by the registry, supplemented when necessary by the participating investigators (e.g., to assure inclusion of ejection fraction data for all patients in the mortality group, even if initially unreported).

Operative mortality was defined as death from any cause within the first 30 days after AICD implantation.

Cause of death was classified as: sudden — death occurring within 1 hour of symptoms in a previously medically stable patient, or death occurring during sleep or unwitnessed; tachyarrhythmic/nonsudden — death associated with sustained ventricular tachyarrhythmias persisting or recurring over a time period longer than 1 hour before death[2]; cardiac nonarrhythmic — witnessed death of a cardiac nature, other than sudden or tachyarrhythmic/nonsudden; cardiac — death that is sudden, tachyarrhythmic/nonsudden, or cardiac nonarrhythmic; and noncardiac — death resulting primarily from other causes. Independent of the Cardiac Pacemakers, Inc. registry, each death and its classification was certified by an investigator at the participating institution.

For patients succumbing to sudden or tachyarrhythmic/nonsudden deaths, the initial recorded rhythm refers to the first known rhythm that could be documented during the terminal event.

**Statistical analysis:** Univariate analyses, consisting of unpaired Student's *t* test and the chi-square test, were applied to the clinical descriptors to test for differences between the operative mortality and reference groups. Multivariate logistic regression analysis was used to search for significant independent predictors of mortality. The Spearman rank test was used to assess the relation between institutional operative mortality and reference group ejection fraction. All p values are based on 2-sided hypothesis tests and are considered statistically significant if $<0.05$.

## RESULTS

Twenty-nine of the 939 patient cohort (3.1%) died within the first 30 days after AICD implantation.

**Analysis of risk factors for operative death (Table I):** There were no statistically significant differences between the mortality and reference groups with regard to age, sex, underlying heart disease, concomitant cardiac surgery, or type of presenting sustained ventricular tachyarrhythmia. However, mean left ventricular ejection fraction was significantly lower in the mortality group than in the reference group, and remained the only significant independent predictor ($p < 0.05$) after multivariate analysis.

**TABLE I** Clinical Descriptors in AICD Implantees

| Descriptor | Operative Mortality Group (n = 29) | Reference Group (n = 219) | p Value* |
|---|---|---|---|
| Age (mean ± SD years) | 58.7 ± 12.7 | 57.5 ± 11.2 | 0.62 |
| Men/women | 26/3 | 175/44 | 0.21 |
| Left ventricular ejection fraction (%) (mean ± SD) | 25.6 ± 10.3 | 33.7 ± 14.8 | <0.001 |
| Underlying heart disease | | | |
| Atherosclerotic (%) | 24 (83) | 166 (76) | 0.76 |
| Nonischemic cardiomyopathy (%) | 3 (10) | 36 (16) | |
| Miscellaneous (%) | 2 (7) | 14 (6) | |
| No known heart disease (%) | 0 (0) | 3 (1) | |
| Concomitant cardiac surgery | | | |
| Performed (%) | 4 (14) | 44 (20) | 0.43 |
| Revascularization alone (%) | 4 (14) | 25 (11) | |
| Resection alone (%) | 0 (0) | 5 (2) | |
| Revascularization and resection (%) | 0 (0) | 14 (6) | |
| Not performed (%) | 25 (86) | 175 (80) | |
| Clinical sustained tachyarrhythmia† | | | |
| Ventricular tachycardia (%) | 17 (59) | 100 (48) | 0.35 |
| Ventricular fibrillation (%) | 1 (3) | 23 (11) | |
| Ventricular tachycardia/fibrillation (%) | 11 (38) | 85 (41) | |

*Unpaired Student's *t* test used for age and left ventricular ejection fraction; chi-square test used for other comparisons.
†n = 208 for reference group.
AICD = automatic implantable cardioverter-defibrillator; SD = standard deviation.

Left ventricular ejection fraction also helped to explain intercenter differences in operative mortality. Among individual institutions, 30-day mortality ranged from 0.0 to 9.4% (median value 2.4%); however, surgeons from centers with higher mortality generally performed implantations in patients with lower left ventricular ejection fraction (Spearman rho $= -0.61$, $p = 0.02$). For the 7 institutions with an operative mortality greater than the median value of 2.4% (pooled operative mortality of 4.6% for 519 implantees), mean left ventricular ejection fraction in 93 reference cases from these institutions was 30 ± 15%. This was significantly lower than the mean ejection fraction of 36 ± 14% ($p < 0.001$) for 126 reference cases from the 8 institutions with operative mortality $\leq 2.4\%$ (pooled operative mortality of 1.2% for 420 implantees).

**Causes of operative death (Figure 1):** Twenty-one of the 29 operative deaths (72%) were cardiac in origin, of which 12 (57%) were sudden or tachyarrhythmic/

nonsudden. Patients who died from cardiac causes had a significantly higher prevalence of atherosclerotic heart disease (95 vs 50%, p = 0.004), and a statistically nonsignificant lower mean left ventricular ejection fraction (23 ± 6 vs 32 ± 15%, p = 0.13) compared with victims of noncardiac death.

**Time to operative death (Figure 2):** Twenty-three (79%) of the 29 fatalities occurred within 2 weeks of implantation, including 6 of 7 sudden and 4 of 5 tachyarrhythmic/nonsudden deaths. All 5 tachyarrhythmic/nonsudden deaths and 4 of 7 sudden deaths occurred before hospital discharge.

**Findings in perioperative sudden and tachyarrhythmic/nonsudden deaths:** Five of the 7 cases of sudden death were monitored, the initial recorded rhythm being ventricular fibrillation in 1 patient and sustained ventricular tachycardia in 3, with degeneration to ventricular fibrillation in 1 of these; electromechanical dissociation was seen in the remaining patient (out-of-hospital death). All 5 tachyarrhythmic/nonsudden deaths were monitored, and the first recorded rhythm was invariably sustained ventricular tachycardia, with degeneration to ventricular fibrillation documented in 1 patient.

Known or likely contributing factors could be identified in 4 cases of sudden death: acceleration of ventricular tachycardia to ventricular fibrillation by the AICD (with ineffective internal and external shocks); interaction with an antitachycardia pacemaker that repeatedly caused degeneration of ventricular tachycardia to ventricular fibrillation (device shocks were initially effective during several rapidly recurring episodes, but eventually became unsuccessful); probable acute ischemia, as evidenced by marked ST-segment elevation on an event monitor recording shortly before death; and acute myocardial infarction documented by autopsy. In 2 tachyarrhythmic/nonsudden deaths, known or likely contributory factors were concomitant congestive heart failure, and a displaced, malsensing transvenous AICD lead with mechanical induction of ventricular tachycardia. With regard to medication, 1 or more antiarrhythmic drugs being administered to 3 patients dying suddenly and 3 patients succumbing to tachyarrhythmic/nonsudden death; 4 of these 6 were receiving amiodarone.

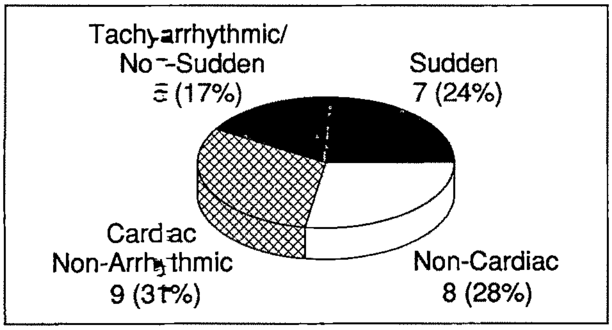

**FIGURE 1. Causes of operative death in 29 patients dying within 30 days after initial implantation of automatic implantable cardioverter-defibrillator.**

At the onset of the patients' terminal events, the AICD had been deactivated since implantation in 2 of 7 sudden (28%) and 3 of 5 tachyarrhythmic/nonsudden deaths (60%). Among those with deactivated devices, the initial recorded rhythm was ventricular tachycardia in all cases. Degeneration to ventricular fibrillation was documented in 1 of the patients who died suddenly; when the device was activated during attempted resuscitation, it failed to defibrillate the patient, and attempted external defibrillation was unsuccessful as well. Delayed AICD activation also occurred in the 4 other patients with initially deactivated devices, but AICD shocks were effective, although transiently, in only 1 patient (recurrent ventricular tachycardia — tachyarrhythmic/nonsudden death). Of the 7 patients with activated devices for whom information was available, AICD shocks were witnessed in 3 of 5 patients who died suddenly, and in both of 2 who succumbed to tachyarrhythmic/nonsudden deaths; the shocks were transiently effective (i.e., failed during tachyarrhythmia recurrence) in 1 case of sudden and 1 case of tachyarrhythmic/nonsudden death.

The reported intraoperative defibrillation threshold was ≤20 J in 4 of 7 sudden and 4 of 5 tachyarrhythmic/nonsudden deaths, with a value of 25 J in the remaining case of tachyarrhythmic/nonsudden death. However, the defibrillation threshold was not measured in 3 patients who died suddenly (terminal ventricular fibrillation documented in 1), all of whom had had sustained ventricular tachycardia as a clinical tachyarrhythmia.

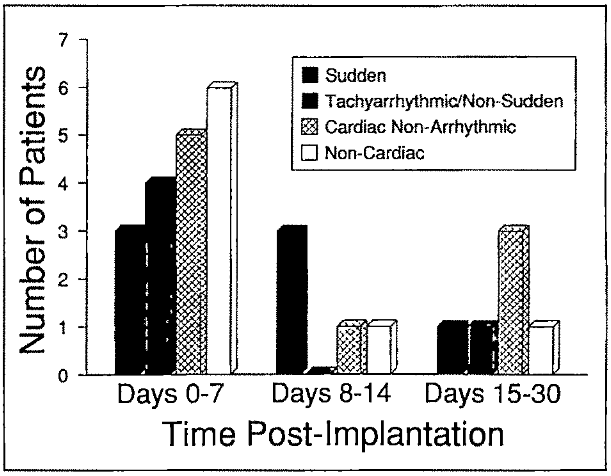

**FIGURE 2. Time to operative death in 29 patients dying within 30 days after initial implantation of automatic implantable cardioverter-defibrillator. Time after implantation is divided into the 3 segments designated on the *abscissa,* and number of patients is shown on the *ordinate.***

## DISCUSSION

In this 939 patient multicenter experience with initial AICD implantation over 6 years, the 30-day operative mortality was 3.1%, which falls within the range of 1.5 to 8.0% reported in smaller published series.[3-12] Our study identifies left ventricular ejection fraction as an independent determinant of operative mortality and draws attention to clinical circumstances surrounding sudden and tachyarrhythmic/nonsudden death within 30 days after AICD implantation.

**Clinical variables related to operative mortality:** Among variables analyzed, left ventricular ejection fraction was the only one found to be significantly different between the operative mortality group and the reference group. Consistent with this finding was the observation that operative mortality by center correlated inversely with the mean reference left ventricular ejection fraction by center.

*Although concomitant surgery did not appear to predict increased operative mortality in our study, this finding is at variance with a recent preliminary report[13] and must be interpreted with caution.* One might rationalize the observed lack of association by postulating a "cancellation effect," in which the increased operative mortality rate expected with cardiopulmonary bypass (and possible aneurysmectomy) superimposed on AICD implantation was counterbalanced by the benefits of revascularization on chronically ischemic myocardium. However, it must be stressed that patients were included in the registry only if an AICD generator was actually implanted. In the setting of concomitant surgery, some patients may have undergone a "2-stage" procedure (lead placement only, followed by generator implantation several days later); if any of these patients died before the intended second stage, they never would have entered the registry. Such a selection bias may have limited our ability to detect an adverse impact of concomitant surgery. Indeed, patients undergoing prophylactic "leads-only" procedures during cardiac surgery have been reported to face an operative mortality as high as 12%.[14]

**Perioperative sudden and tachyarrhythmic/nonsudden death:** In this series, sudden and tachyarrhythmic/nonsudden death accounted for 24 and 17%, respectively, of the 30-day operative mortality. Sustained ventricular tachycardia or ventricular fibrillation was observed in the majority of sudden deaths for which electrocardiographic monitoring was available during the terminal event; by definition, these arrhythmias were documented in all cases of tachyarrhythmic/nonsudden death. Except for 1 patient in whom transvenous ventricular sensing lead dislodgement led to both repetitive ventricular tachycardia induction and device malfunction, AICD shocks in cases of tachyarrhythmic/nonsudden death were typically delivered appropriately (when devices were activated) with initial success; however, repeated bouts of sustained ventricular tachycardia or ventricular fibrillation, or both, ultimately proved fatal.

The context for the occurrence of perioperative sudden death in this large series of AICD implantees suggests that, in at least some cases, management factors may not have given the device the "best chance" of working. Among these factors in the 7 sudden death cases were the absence of defibrillation threshold testing in 3 patients (one of whom had ventricular fibrillation documented during his terminal event), and postoperative device deactivation in 2. The former, historically, may have reflected a belief in some centers that defibrillation threshold testing was not necessary for patients presenting with sustained ventricular tachycardia.

During the time period of our study, device deactivation immediately after implantation was frequently performed as a means of preventing shocks triggered by possible postoperative atrial tachyarrhythmias. Consistent with our observations, a recent survey documented the occurrence of at least 1 postoperative sudden (tachyarrhythmic) death associated with a deactivated AICD in 4 of 28 (14%) implanting institutions.[15] Clearly, a cause-and-effect relation is difficult to establish in these cases, and complementary information is needed concerning device activation status in operative survivors. Nonetheless, the greater probability of time delays before attempted electrical conversion or defibrillation, and the potential for electrical impedance to be increased by myocardial patch electrodes,[16] support the contention that failure to maintain device activation postoperatively may reduce the likelihood of successful resuscitation during tachyarrhythmic cardiac arrest.

Evidence of myocardial ischemia or infarction was present in 2 cases of sudden death (both out-of-hospital), pointing to the possible role of underlying substrate changes. Antiarrhythmic drugs (primarily amiodarone) may have had a potentiating effect in some of the perioperative sudden or tachyarrhythmic/nonsudden deaths, either through a proarrhythmic mechanism[17] or through elevation of the defibrillation threshold.[18-20] However, the design of our study does not permit us to draw conclusions with regard to these issues. On the other hand, "device proarrhythmia" was clearly documented in 3 patients (ventricular fibrillation or ventricular tachycardia induced by an AICD shock, antitachycardia pacemaker, or the mechanical effect of a displaced transvenous sensing lead).

**Study limitations:** Given the retrospective nature of our study, the 30-day mortality figure of 3.1% after initial AICD implantation may have been skewed by a variety of influences. As noted previously, "true" operative mortality may have been underestimated by the exclusion of patients dying before completion of a 2-stage implantation. Conversely, our 3.1% figure could have been inflated by the inclusion of patients destined to die independent of AICD implantation. More accurate operative mortality data must await large prospective, randomized clinical trials where early death rates can be compared in groups treated with and without devices using an intention-to-treat analysis. Such trials will also help to assess the role, if any, of specific factors, such as functional class, concomitant surgery and history of cardiac surgery.

As described previously (see Methods), the reference group of operative survivors represented only a subset of the entire implantation cohort, selected by virtue of an ejection fraction value being reported to the registry. However, the similarity of the mean left ventricular ejection fraction (33.7%) in our reference group to that reported in other series of AICD implantees,[6-8,10,12] as well as the wide variability of left ventricular ejection fraction data, argue against any significant selection bias in our reference group.

This investigation also may be limited by a historical bias, in that implantation techniques, intraoperative testing protocols, postoperative practices and device features have continued to evolve beyond the study period. For example, defibrillation threshold testing during implantation is now routinely performed and recommended, regardless of the presenting tachyarrhythmia.[15,21] Moreover, current availability of cardioverter-defibrillators that are programmable allows for immediate postimplant activation with a temporary high rate cutoff, thereby permitting prompt device intervention for rapid ventricular tachycardia or ventricular fibrillation, while also reducing the likelihood of shocks being triggered by postoperative atrial tachyarrhythmias. Nonetheless, "learning curve" issues are likely to have a persistent impact on operative mortality as increasing numbers of medical centers initiate implantation programs; device-related aggravation of sustained ventricular tachyarrhythmias remains a potential cause of perioperative sudden death, perhaps even more so with the advent of programmable devices.[22]

Finally, operative mortality (especially that resulting from nonarrhythmic cardiac and noncardiac causes) is likely to decrease over the coming years as nonthoracotomy devices[23] become more widely available. However, defibrillation threshold requirements may still oblige a significant proportion of device therapy candidates to undergo a thoracotomy-type implantation. Thus, our findings should continue to be relevant to these patients and, as such, may provide an upper limit estimate for operative mortality in the future.

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## APPENDIX

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# Hemodynamic Comparison of Two Nifedipine Formulations in Patients with Essential Hypertension

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**The hemodynamic and humoral effects and trough-to-peak 24-hour blood pressure responses of 2 nifedipine formulations, capsules and continuous-release once-daily formulation tablets, were evaluated in 10 patients with mild to moderate essential hypertension. Both formulations reduced mean arterial pressure similarly from 120 ± 3 (baseline) to 107 ± 2 ($p < 0.005$) and 105 ± 2 mm Hg ($p < 0.005$) and total peripheral resistance index from 65 ± 9 (baseline) to 47 ± 4 ($p < 0.05$) and 45 ± 3 U/m$^2$ ($p < 0.05$), respectively. Renal, splanchnic and total forearm (including skin and skeletal muscle) blood flows were maintained or even increased slightly associated with reductions in regional vascular resistances. Decreases in renal, total forearm and skeletal muscle resistances were significant ($p < 0.05$) with the capsules, but the decrease was only significant in renal resistance with the long-acting tablets. Intravascular volume did not expand with reduction in arterial pressure. This antihypertensive effect was not related to baseline plasma renin activity levels or age. Nifedipine tablets provided a better control of mean arterial pressure (65%) than did capsules (44%).**

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Since their clinical introduction,[1] calcium antagonists have gained extensive use for antihypertensive treatment,[2,3] and they are now included among the first-line therapeutic agents for the initial treatment of hypertension.[4] Nifedipine, a dihydropyridine derivative, has been used as an antihypertensive agent in both tablet and capsular formulation[5–7]; the slow-release formulation has been available recently for once-daily use. This study was designed to compare the systemic and regional hemodynamic effects of the slow-release tablet with the capsular formulations.

## METHODS

**Patients:** Ten patients (9 men, 5 white) with mild to moderately severe essential hypertension, whose ages ranged from 39 to 71 years (average 52 ± 3), were studied. Patients were enrolled if their supine diastolic pressure was 90 to 115 mm Hg after discontinuation of all medication for ≥4 weeks. Informed consent, previously approved by our institutional clinical investigation committee, was obtained from all patients before entrance into the study.

**Studies:** The study consisted of 4 monotherapeutic phases: phase I, the capsule (10 to 40 mg 3 times a day, average 55.5 mg/day) of ≥4 weeks' duration; phase II, 2-week placebo washout period; phase III, titration to goal diastolic pressure (<90 mm Hg or ≥10 mm Hg reduction in diastolic pressure) administering 30 to 150 mg of nifedipine tablet formulation administered once daily; and phase IV, nifedipine tablet maintenance therapy (average 64.7 mg/day) for 8 weeks. All hemodynamic and laboratory studies were performed at the end of phases I, II and IV, and all 24-hour pressure recordings were obtained on the day before the completion of that phase of study.

**Blood pressure measurements:** Blood pressure measurements were obtained before prescribing the next dose of medication (8 hours after receiving nifedipine capsules and approximately 24 hours after receiving the nifedipine long-acting, once-daily tablets). In addition, 24-hour ambulatory blood pressure monitor records were also obtained in 8 patients (Accutracker, Suntech, Raleigh, North Carolina). The average number of blood pressure recorder readings were 135 ± 2, 133 ±

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2 and 138 ± 1 mm Hg for each patient during phases I, II and IV, respectively; 89, 89 and 87% of these recordings were valid for interpretation. Blood pressure and heart rate were measured for the entire 24-hour period and were then subdivided into six 4-hour periods for statistical analysis and comparison.

**Echocardiography:** Two-dimensional guided M-mode echocardiograms (Toshiba, SSH 60-A, 2.5 and 3.75 MHz) were obtained to determine resting cardiac anatomic and functional indexes. Three echocardiograms, obtained at the conclusion of phases I, II and IV in all patients, were interpreted by 2 independent observers who were unaware of the phase of study for the respective patients. Patients were studied in the recumbent, half-left, lateral position.

Left ventricular wall thickness and dimensions were measured according to standard criteria.[8] Left ventricular volumes were calculated according to the Teichholz formula,[9] and left ventricular mass (American Society of Electrocardiography cube formula) was corrected as proposed by Devereux et al.[10] Cardiac output was calculated as the product of heart rate and stroke volume (end-diastolic minus end-systolic volume), and total peripheral resistance was calculated by dividing mean arterial pressure (diastolic pressure plus one-third of pulse pressure) by cardiac output. Ventricular preload was assessed as end-diastolic volume divided by body surface area, and afterload as end-systolic wall stress.[11]

Left ventricular systolic function was estimated by calculating ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening and the contractility index (end-systolic wall stress/end systolic volume index). Diastolic function was determined by computer analysis of digitized echograms of the septum and posterior left ventricular endocardial wall using a point preceding 1 R wave to the subsequent point of the succeeding R wave. Continuous plots of left ventricular minor axis dimension versus time or the rate of dimensional change versus time were obtained. In this manner, for each patient 3 to 5 echocardiographic cycles were analyzed and averaged. Peak filling rate (PFR) was corrected for diastolic dimension (DD) in order to achieve the normalized peak filling rate (nPFR) [$nPFR = PFR/(DD \cdot 0.8)$], and duration (DUR) of rapid filling was corrected (cDUR) for heart rate [$cDUR = DUR \cdot (\text{heart rate}/60)$].[12]

**Regional hemodynamics:** Renal blood flow was determined by measuring iodine-131 para-aminohippuric acid clearance.[13,14] Glomerular filtration rate was determined from endogenous creatinine clearance. Splanchnic blood flow was calculated from clearance of injected indocyanine green dye.[15] Total forearm blood flow, with estimation of skin and skeletal muscle flow and resistances, was obtained from the increase in forearm volume during venous occlusion with and without hand exclusion using a mercury-filled Silastic strain-gauge plethysmograph.[16,17]

**TABLE I** Hemodynamic Indexes and Plasma Catecholamines Produced by Two Formulations of Nifedipine

| | Capsules | Placebo | Tablets |
|---|---|---|---|
| Mean arterial pressure (mm Hg) | 107 (2)† | 120 (3) | 105 (2)† |
| Heart rate (beats/min) | 73 (3) | 68 (2) | 74 (4) |
| Stroke volume index (ml/beat/m²) | 34 (2) | 31 (3) | 34 (2) |
| Cardiac index (liters/min/m²) | 2.47 (0.2) | 2.08 (0.2) | 2.51 (0.2) |
| Total peripheral resistance index (U/m²) | 47 (4)* | 65 (9) | 45 (3)* |
| Total blood volume (ml) | 5,568 (224) | 5,496 (228) | 5,669 (249) |
| Plasma volume (ml) | 3,323 (118) | 3,255 (160) | 3,418 (180) |
| Norepinephrine (pg/ml) | 467 (91) | 387 (71) | 375 (60) |
| Epinephrine (pg/ml) | 35 (7) | 31 (5) | 28 (4) |
| Plasma renin activity (ng/ml/hour) | 1.9 (0.30) | 1.7 (0.4) | 1.5 (0.4) |

*$p < 0.05$; †$p < 0.005$ with respect to placebo value.
Data are mean ±1 standard error of the mean.

**Intravascular volumes and humoral measurements:** Plasma volume was measured with iodine-125 human serum albumin.[13] Total blood volume was calculated from plasma volume and hematocrit (total blood volume = plasma volume/(1 − hematocrit). Plasma levels of circulating norepinephrine and epinephrine were measured radioenzymatically from venous blood withdrawn 30 minutes after supine resting.[18] Plasma renin activity was measured by radioimmunoassay.[19]

**Statistics:** One-way analysis of variance with repeated measurements was used to establish statistical significance[20] with subsequent pairwise comparison. All data are presented as mean ± 1 standard error of the mean.

## RESULTS

Both nifedipine formulations, capsules and tablets, reduced laboratory and office arterial pressures (systolic, diastolic and mean) significantly with average daily doses of 55.5 and 64.7 mg/day, respectively (Tables I and II). During hemodynamic evaluation, mean arterial pressure was significantly reduced (−13 mm Hg for capsules $p < 0.005$; −15 mm Hg for tablets $p < 0.005$) with both active treatment formulations as compared with the placebo period, and this was associated with significant reduction in total peripheral resistance (indexes) ($p < 0.05$) (Table I). Heart rate and cardiac index in the hemodynamic evaluation showed no significant differences between the first (capsule), second (placebo), and third (tablets) hemodynamic studies (Table I). However, office heart rate in the upright position was faster during both treatment phases than during the placebo phase. However, in the supine posi-

**TABLE II** Office Blood Pressure and Heart Rate Determinations During Three Treatment Phases

| | Supine | | | Standing (1 min) | | |
|---|---|---|---|---|---|---|
| | Capsules | Placebo | Tablets | Capsules | Placebo | Tablets |
| Systolic | 134 (3)† | 159 (5) | 139 (3)* | 134 (3)† | 156 (5) | 136 (5)* |
| Diastolic | 85 (2)† | 101 (3) | 90 (2)† | 85 (3)† | 103 (3) | 91 (3)† |
| Mean | 101 (2)† | 120 (3) | 106 (1)† | 101 (3)† | 121 (3) | 106 (3)† |
| Heart rate (beats/min) | 79 (2)† | 70 (2) | 74 (2) | 81 (2)† | 71 (2) | 79 (2)‡ |

*p <0.05; †p <0.005; ‡p <0.001, compared with placebo value.
Data are mean ± 1 standard error of the mean.

**TABLE III** Regional Hemodynamic Measurements

| | Capsules | Placebo | Tablets |
|---|---|---|---|
| Renal | | | |
| Blood flow (ml/min) | 902 (91)* | 753 (93) | 798 (73) |
| Vascular resistance (U) | 14 (2)* | 20 (4) | 15 (2)* |
| Glomerular filtration rate (ml/min) | 128 (11)* | 114 (10) | 120 (10) |
| Filtration fraction (%) | 15 (1) | 17 (2) | 15 (1) |
| Splanchnic | | | |
| Blood flow (ml/min) | 876 (112) | 964 (137) | 912 (167) |
| Vascular resistance (U) | 17 (4) | 15 (2) | 14 (2) |
| Forearm | | | |
| Total forearm blood flow (ml/min) | 7.0 (0.4) | 6.2 (0.7) | 7.2 (0.7) |
| Total forearm vascular resistance (U) | 15.9 (1.1)* | 22.0 (2.6) | 15.6 (1.3) |
| Skeletal muscle blood flow (ml/min/100 g) | 5.7 (0.4) | 4.8 (0.5) | 5.7 (0.4) |
| Skeletal muscle vascular resistance (U) | 20 (1.4)† | 28 (3.3) | 20 (1.5) |
| Skin blood flow (ml/min/100 g) | 1.3 (0.1) | 1.4 (0.2) | 1.6 (0.3) |
| Skin vascular resistance (U) | 100 (15.3) | 114 (19.6) | 84 (13.7) |

*p <0.05; †p <0.02.
Data are mean ± 1 standard error of the mean.

tion, only the capsular formulation increased heart rate (Table II).

**Regional hemodynamics:** Renal blood flow increased with the capsular formulation compared with placebo, but this was not observed with the tablet formulation (Table III). However, renal vascular resistance was similarly and significantly reduced with both formulations (p <0.05). Glomerular filtration rate increased significantly only with the capsular formulation. There were no significant changes in renal filtration fraction with either nifedipine formulation.

Total forearm blood flow as well as skin and skeletal muscle blood flow increased slightly but insignificantly. However, total forearm vascular and skeletal muscle vascular resistances decreased significantly only with the capsular formulation. The difference with respect to the long-acting tablet formulation reflects a greater standard error in that group. Splanchnic blood flow decreased slightly (but insignificantly) during both treatment periods. As a result, both nifedipine formulations reduced renal, splanchnic and forearm resistance (including skeletal muscle and cutaneous vascular resistances), but only renal vascular resistance decreased significantly with both drug formulations (Table III).

**Twenty-four-hour pressures:** The average 24-hour blood pressure records obtained during the placebo phase (149 ± 3/90 ± 3 mm Hg) were significantly reduced with nifedipine capsules and tablets (140 ± 2/84 ± 2 and 138 ± 3/81 ± 2 mm Hg, respectively). The tablet demonstrated a more even and steady control of both systolic and diastolic pressures throughout the 24-hour period compared with the capsules (Table IV). With the tablet formulation, mean arterial pressure reduction was maximal (12%) between 6 and 10 A.M., with the least decline (8%) observed between 10 P.M. and 2 A.M. The capsules produced a comparable maximal pressure reduction (12%) between 6 and 10 A.M., and the trough effect was 5% during the 12-hour period between 10 A.M. and 10 P.M. Thus, the reduction in arterial pressure was smooth for the tablet and capsular formulations, and early morning control seemed to be better.

**Humoral changes:** Epinephrine, norepinephrine and plasma renin activity each declined insignificantly from the first to the second and third hemodynamic evaluation. Moreover, no significant relation was seen between reduction in arterial pressure (office or laboratory) and the change in these humoral measurements with respect to the age of the patients.

**Echocardiographic measurements:** Left ventricular mass, septal and posterior wall thicknesses, and diastolic dimension as well as the variety of indexes of ventricular function did not differ during the 3 treatment phases (Table V).

## DISCUSSION

The results of this study confirm previous reports demonstrating the antihypertensive effectiveness of nifedipine capsules[6,7] and extend this conclusion to the newer single daily dose of an osmotic pump formulation (nifedipine tablets) that provides a more even and steady control of pressure over the entire 24-hour period. Moreover, trough-to-peak ratio in pressure reduc-

**TABLE IV** Systolic and Diastolic Pressure Reduction After Treatment with Nifedipine Capsules and Tablets (averages for 24 hours and for six four-hour intervals)

| | 24 Hours | 5–10 A.M. | 10–2 P.M. | 2–6 P.M. | 6–10 P.M. | 10–2 A.M. | 2–6 A.M. |
|---|---|---|---|---|---|---|---|
| Capsules | | | | | | | |
| Systolic | 140 (2) | 140 (2)‡ | 142 (2) | 141 (2) | 137 (3) | 131 (5)* | 132 (5)* |
| Diastolic | 84 (2)‡ | 85 (2)‡ | 87 (3) | 86 (2) | 88 (3) | 76 (4)* | 81 (4) |
| Mean | 103 (2)† | 102 (2)‡ | 105 (2) | 105 (2) | 107 (2) | 94 (4)* | 98 (4)* |
| Placebo | | | | | | | |
| Systolic | 149 (3) | 155 (2) | 148 (5) | 151 (5) | 152 (3) | 141 (3) | 143 (4) |
| Diastolic | 90 (3) | 97 (3) | 93 (4) | 91 (4) | 95 (4) | 82 (2) | 86 (3) |
| Mean | 110 (3) | 116 (2) | 111 (4) | 111 (4) | 113 (3) | 101 (2) | 104 (3) |
| Tablets | | | | | | | |
| Systolic | 138 (3)† | 139 (3)* | 143 (3) | 141 (3) | 143 (3) | 130 (6)* | 131 (4)‡ |
| Diastolic | 81 (2)† | 84 (2)‡ | 84 (2)* | 80 (2)* | 83 (2)* | 74 (3) | 77 (3)† |
| Mean | 100 (2)† | 102 (3)‡ | 103 (2)* | 100 (2)* | 103 (2)* | 93 (4)* | 95 (3)† |

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$.
Data are mean ± 1 standard error of the mean.

tion was superior with the once-daily tablet formulation (66%) compared with the 3 times-daily capsular formulation (44%). Trough levels (−5%) of blood pressure reduction were seen in 3 of six 4-hour intervals compared with only one 4-hour period with a trough reduction of −8% with the tablet formulation. The average mean arterial pressure reduction achieved with the 2 nifedipine formulations ranged from 5 to 12%, a finding that is in agreement with earlier reports.[21]

Both formulations of nifedipine reduced total forearm (cutaneous and skeletal muscle) and renal vascular resistances and increased skeletal muscle and renal blood flows. The capsular formulation increased renal blood flow and glomerular filtration rate and reduced the renal, skeletal muscle and total forearm vascular resistance. Only renal vascular resistance significantly decreased during treatment with long-acting tablets (Table III). These renal hemodynamic findings agree with previous studies using nifedipine.[22] However, diltiazem[23] and nitrendipine[24] increased renal flow and verapamil[25] maintained renal flow. Nevertheless, each of these agents reduced renal vascular resistance. Only diltiazem and nitrendipine decreased the renal filtration fraction.[23,24]

In this study, preload measured by echocardiography remained unchanged. We were unable to detect any significant change in systolic (stroke volume, fractional fiber shortening, velocity of circumferential fiber shortening, ejection fraction) or diastolic (normalized peak filling rate, duration of rapid filling corrected for heart rate) functions. This also includes end-systolic wall stress to end-systolic volume index ratio, a sensitive, relatively lead-independent index of cardiac contractility (Table V).[26] It is clear that the 2-week placebo period was insufficient to show any changes in cardiac chamber structure with either form of therapy.

**TABLE V** Left Ventricular Function and Structure

| | Capsules | Placebo | Tablets |
|---|---|---|---|
| Systolic function | | | |
| Ejection time, corrected (ms) | 315 (9) | 304 (7) | 299 (5) |
| Fractional fiber shortening (%) | 33 (1) | 30 (2) | 33 (2) |
| Ejection fraction (%) | 62 (2) | 57 (3) | 60 (3) |
| Velocity circumferential fiber shortening (circ/s) | 1.07 (0.1) | 1.01 (0.1) | 1.10 (0.1) |
| Contractility (U) | 2.16 (0.1) | 2.24 (0.1) | 2.09 (0.1) |
| Diastolic function | | | |
| Peak filling rate (1/sec) | 1.9 (0.2) | 2.1 (0.3) | 2.1 (0.25) |
| Duration rapid filling, corrected (ms) | 262 (12) | 272 (14) | 292 (26) |
| Loading conditions | | | |
| Preload (end-diastolic volume; U/m$^2$) | 55 (3.8) | 54 (4.2) | 57 (3.4) |
| Afterload (end-systolic wall stress; 10$^3$ dynes/cm$^2$) | 46 (4.3) | 51 (4.2) | 47 (4.7) |
| Left ventricle | | | |
| Septal thickness (cm) | 1.20 (0.05) | 1.18 (0.05) | 1.16 (0.04) |
| Posterior wall thickness (cm) | 1.10 (0.04) | 1.12 (0.03) | 1.09 (0.03) |
| Diastolic dimension (cm) | 4.95 (0.2) | 4.86 (0.2) | 5.01 (0.2) |
| LV mass index (g/m$^2$) | 102 (5) | 101 (6) | 102 (4) |

Data are mean ± 1 standard error of the mean.
LV = left ventricular.

Finally, neither formulation of nifedipine produced fluid retention as evidenced by constant levels of total blood and plasma volumes and body weights throughout the trial. This finding is consistent with that measurement reported previously.[27]

Therefore, we conclude that both formulations of nifedipine were effective in reducing elevated arterial pressure. The once-daily slow-release formulation (tablets) was as effective in controlling elevated arterial pressures throughout a 24-hour time period as the 3-times-daily capsular formulation. Renal vascular resistances were reduced with both formulations although only the capsular form increased renal flow.

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# Effect of Nifedipine Tablets on Ambulatory Blood Pressure in Patients Aged <60 and >65 Years with Systemic Hypertension

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**To evaluate the effect of age on the pattern of circadian blood pressure after nifedipine tablets, ambulatory blood pressure after administration of low and high doses of nifedipine, taken twice daily, was measured over a 24-hour period in 10 elderly and 8 young hypertensive patients. After a 2-week control period without antihypertensive drug, 10 mg of nifedipine was administered twice daily for 2 weeks (low-dose period), followed by 2 weeks of 20 mg (high-dose period). At the end of each period, ambulatory BP monitoring was conducted every 30 minutes for 24 hours, using an ABPM 630 (Nippon-Colin, Komaki, Japan). In both groups, averages of systolic and diastolic BP for the entire day decreased significantly from the control to the low-dose periods. However, after the high-dose period, only the elderly group had further significant reduction of systolic BP, whereas no further reduction was seen in the young group. Separate analysis of whole-day data into daytime and nighttime values revealed that a further decrease in systolic BP after the high-dose period in the elderly group was a reflection of nighttime decline. It was suggested that circadian BP patterns after administration of nifedipine tablets in the elderly differed from those in young hypertensive patients, especially after administration of the high-dose.**

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The recent introduction of the noninvasive ambulatory blood pressure (BP) monitoring technique into the clinical field has provided a great amount of information concerning changes in circadian patterns of BP after administration of antihypertensive agents.[1-4] However, the age of subjects has not been taken into consideration in most of these studies. It is conceivable that the circadian pattern of BP after antihypertensive agents in the elderly differs from that of younger patients because of age-related pharmacokinetic and pathophysiologic changes. The present study evaluates whether the BP-lowering effects of nifedipine tablets, administered twice daily, differ over a 24-hour period in elderly and younger hypertensives.

## METHODS

**Study patients:** Eighteen outpatients with mild or moderate hypertension were recruited for the study. These patients were divided into 2 groups according to age: group 1 consisted of 10 patients >65 years old (mean age 70) and group 2 consisted of 8 cases <60 years of age (mean age 49). Hypertension was defined as ≥160 mm Hg systolic BP in the clinic, or ≥90 mm Hg diastolic BP in 2 of 3 BP measurements at the clinic. Secondary hypertension was ruled out by routine examination. All patients were diagnosed as class I or II hypertensives according to the classification of the World Health Organization.

**Protocol:** The protocol of the study consisted of 3 phases: a 2- to 4-week control period in which any antihypertensive agents were withdrawn; a low-dose period, in which nifedipine tablets were given at a dose of 10 mg twice a day, at 0800 and 2000 hours for 2 weeks (treatment 1, low-dose period); a high-dose period, in which nifedipine tablets were administered at a dose of 20 mg twice a day for 2 weeks (treatment 2, high-dose period). Patients visited the clinic every 2 weeks for BP measurement.

**Ambulatory blood pressure monitoring:** At the end of each period, ambulatory BP and pulse rate monitoring were conducted noninvasively at half-hour intervals over 24 hours using an automated portable recorder (ABPM 630, Nippon Colin, Komaki) that recorded os-

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**TABLE I** Changes in Blood Pressure and Pulse Rate in the Clinic

| | Control (1) | Treatment 1 (2) | Treatment 2 (3) | (1) vs (2) | (1) vs (3) | (2) vs (3) |
|---|---|---|---|---|---|---|
| Young group | | | | | | |
| Systolic BP (mm Hg) | 175 ± 8 | 143 ± 16 | 133 ± 11 | † | * | NS |
| Diastolic BP (mm Hg) | 101 ± 15 | 88 ± 9 | 77 ± 9 | † | * | † |
| Pulse rate (beats/min) | 69 ± 5 | 70 ± 3 | 74 ± 2 | NS | NS | NS |
| Elderly group | | | | | | |
| Systolic BP (mm Hg) | 172 ± 12 | 153 ± 19 | 140 ± 23 | * | * | † |
| Diastolic BP (mm Hg) | 91 ± 7 | 79 ± 10 | 68 ± 11 | * | * | † |
| Pulse rate (beats/min) | 71 ± 8 | 78 ± 12 | 80 ± 8 | NS | NS | NS |

*p <0.05; †p <0.01.
BP = blood pressure; NS = not significant.

cillometric signals. All recordings of ABPM were performed on weekdays to avoid differences of daily life activity between each of the periods. The 24-hour BP data were divided into daytime (600 to 2100 hours) and nighttime (2130 to 0530 hours) values for analysis.

**Statistical analysis:** Student's paired *t* tests were used for comparisons of the data between each period. A probability value <5% was taken to be significant. All values were expressed as mean ± standard deviation.

## RESULTS

**Blood pressure in the clinic (Table I):** In both groups, significant reductions in systolic and diastolic BP in the clinic were observed between the control and low-dose periods (p <0.05) or the high-dose period (p <0.01). Systolic BP in the high-dose period was significantly lower than that in the low-dose period in the elderly group (p <0.05), but not in the younger group (p = not significant).

**Ambulatory blood pressure measurements:** YOUNGER GROUP (FIGURE 1): In the control period, circadian changes in BP increased during the day and decreased at night. In the low-dose period, reductions in systolic and diastolic BPs were observed, beginning 1 hour after nifedipine administration and continuing for about 7 to 8 hours. However, no further decline in either systolic or diastolic BP was seen in the high-dose period.

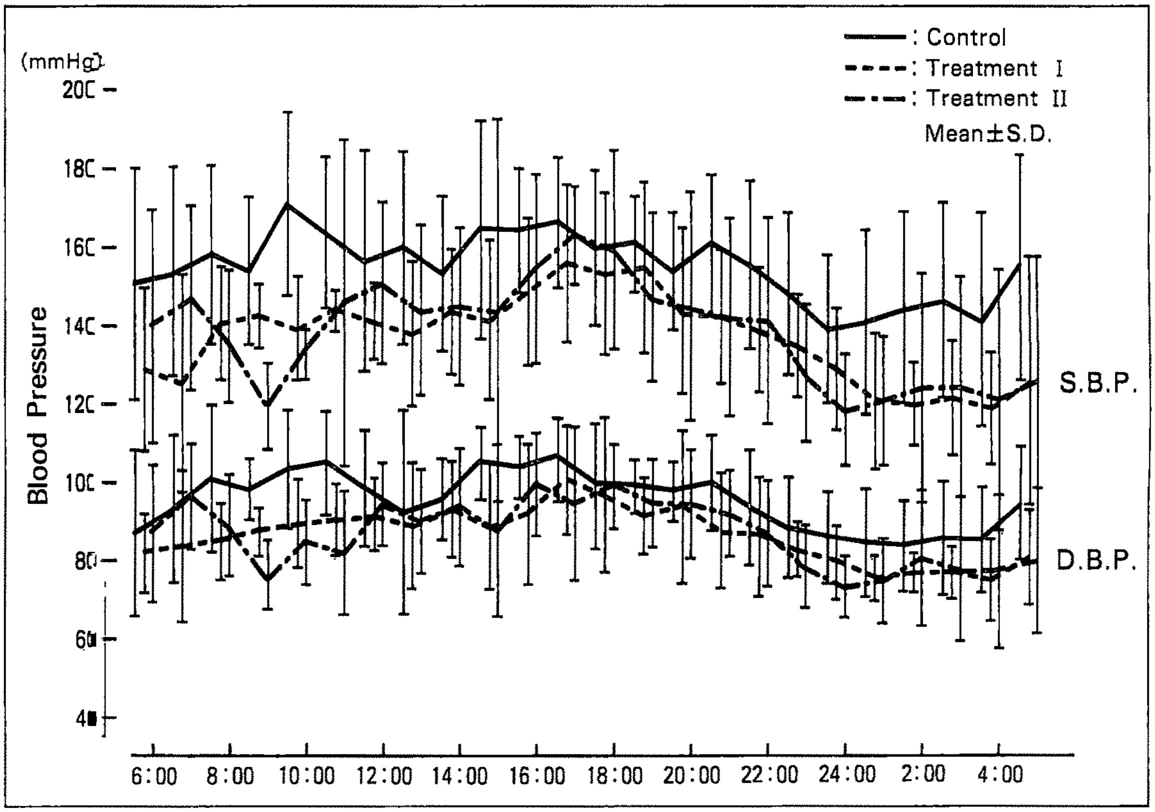

**FIGURE 1. Twenty-four-hour blood pressure monitoring in the young hypertensive group during each period. D.B.P. = diastolic blood pressure; S.B.P. = systolic blood pressure; S.D. = standard deviation.**

**TABLE II** Changes in Blood Pressure and Pulse Rate in a Complete Day, Daytime and Nighttime

| | | Control (1) | Treatment 1 (2) | Treatment 2 (3) | (1) vs (2) | (1) vs (3) | (2) vs (3) |
|---|---|---|---|---|---|---|---|
| | | | Whole Day | | | | |
| Young | Systolic BP | 156 ± 14 | 138 ± 11 | 139 ± 18 | * | * | NS |
| | Diastolic BP | 96 ± 8 | 87 ± 9 | 88 ± 10 | † | † | NS |
| | Pulse rate | 71 ± 11 | 75 ± 13 | 80 ± 8 | NS | † | † |
| Elderly | Systolic BP | 160 ± 16 | 145 ± 12 | 135 ± 15 | * | * | † |
| | Diastolic BP | 84 ± 6 | 77 ± 4 | 74 ± 5 | * | * | † |
| | Pulse rate | 68 ± 8 | 72 ± 8 | 71 ± 7 | NS | NS | NS |
| | | | Daytime — 600 to 2100 Hours | | | | |
| Young | Systolic BP | 160 ± 15 | 143 ± 14 | 145 ± 16 | † | † | NS |
| | Diastolic BP | 100 ± 9 | 91 ± 11 | 92 ± 9 | NS | † | NS |
| | Pulse rate | 75 ± 13 | 79 ± 12 | 87 ± 9 | NS | † | NS |
| Elderly | Systolic BP | 163 ± 14 | 150 ± 10 | 141 ± 15 | * | * | NS |
| | Diastolic BP | 86 ± 5 | 80 ± 5 | 77 ± 6 | * | * | NS |
| | Pulse rate | 72 ± 9 | 77 ± 9 | 75 ± 8 | NS | NS | NS |
| | | | Nighttime — 2130 to 530 Hours | | | | |
| Young | Systolic BP | 147 ± 19 | 128 ± 11 | 127 ± 23 | † | † | NS |
| | Diastolic BP | 89 ± 10 | 80 ± 7 | 80 ± 13 | † | † | NS |
| | Pulse rate | 62 ± 11 | 68 ± 15 | 68 ± 7 | NS | NS | NS |
| Elderly | Systolic BP | 154 ± 24 | 135 ± 18 | 124 ± 17 | * | * | * |
| | Diastolic BP | 78 ± 10 | 70 ± 7 | 66 ± 7 | * | * | NS |
| | Pulse rate | 60 ± 9 | 62 ± 7 | 62 ± 8 | NS | NS | NS |

*p <0.01; †p <0.05.
Abbreviations as in Table I.

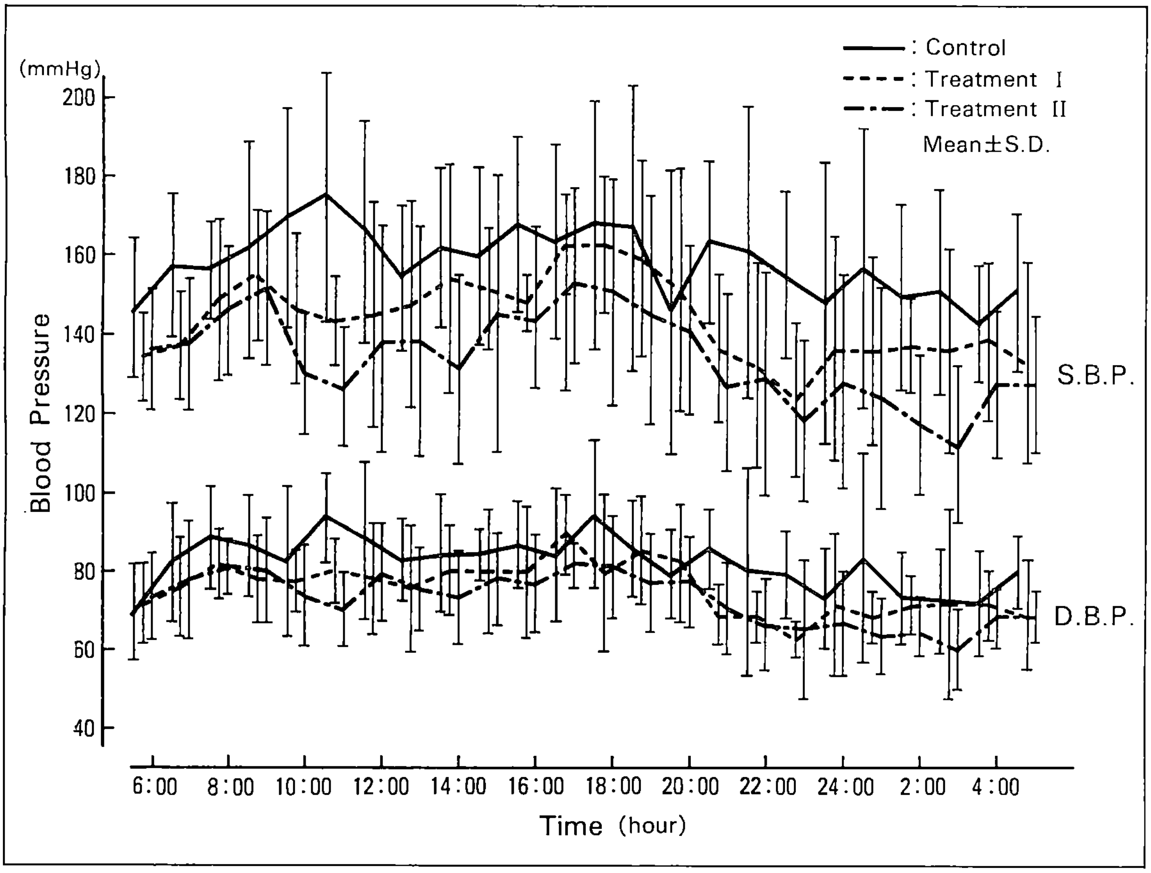

**FIGURE 2. Twenty-four-hour blood pressure monitoring in the elderly hypertensive group during each period. Abbreviations as in Figure 1.**

ELDERLY GROUP (FIGURE 2): For the elderly group, the pattern of circadian change in systolic BP in the control period appeared to be similar to that for the younger group. In the low-dose period, systolic BP decreased, lasting for 7 to 8 hours after taking nifedipine. Further reductions in systolic BP were observed in the high-dose period, especially at 1100 or 0300 hours.

**Whole-day, daytime and nighttime blood pressure (Table II and Figure 3, A and B):** YOUNGER GROUP: The whole-day average of systolic BP in the control period significantly decreased in the low-dose ($p < 0.01$) and high-dose ($p < 0.01$) periods, but no significant reductions were observed between the low-dose and high-dose periods. Diastolic BP change was similar to the change in systolic BP. Pulse rate significantly increased from the control to the high-dose periods, whereas no significant change was seen in the low-dose period.

Daytime and nighttime reductions in BP showed comparable changes with the whole-day values; daytime or nighttime averages of systolic and diastolic BP significantly decreased from the control to the low-dose period. However, no further declines in BP were seen

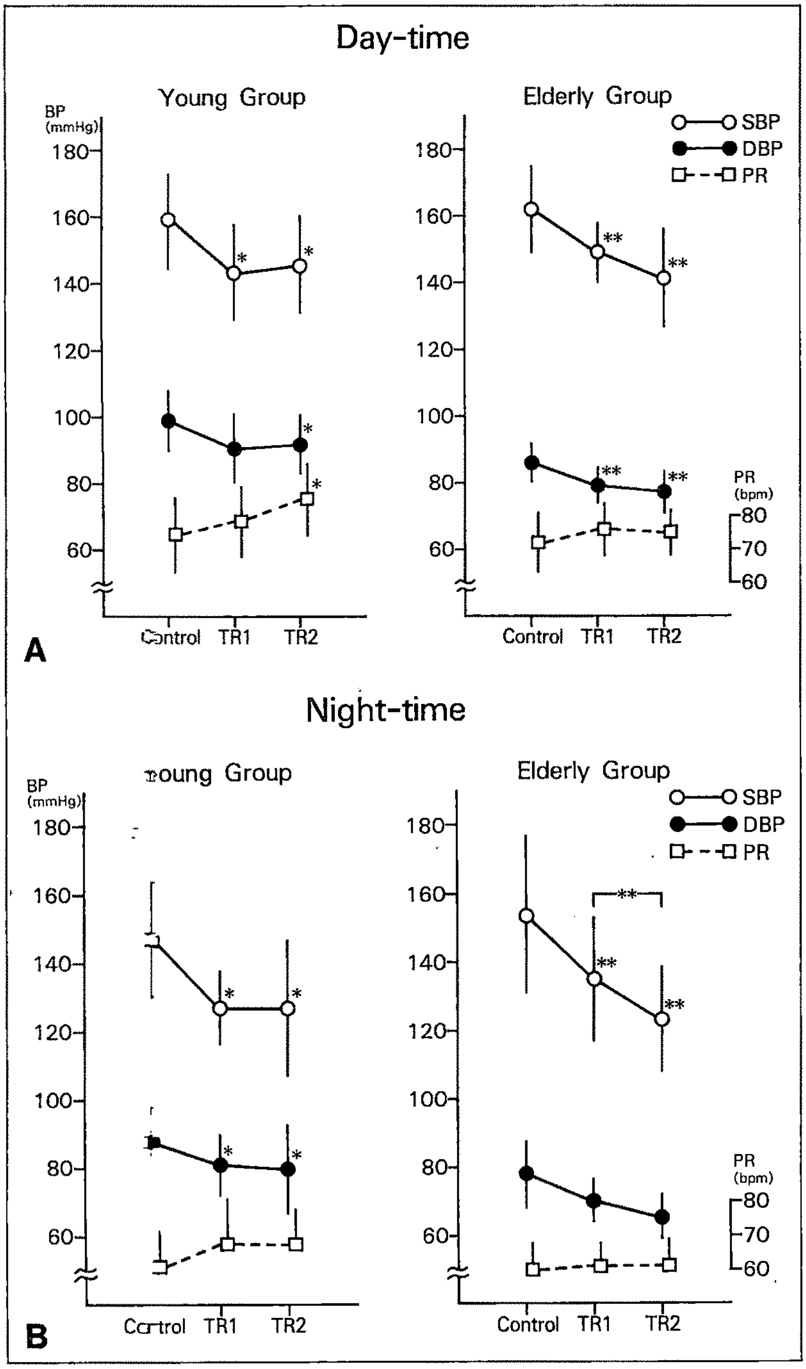

**FIGURE 3. Changes of average blood pressure and pulse rate (PR) after treatments 1 (TR1) and 2 (TR2) in the young and elderly groups. *A*, daytime (600 to 2100 hours); *B*, nighttime (2130 to 530 hours). Values are expressed as mean ± standard deviation. Abbreviations as in Figure 1. *$p < 0.05$; **$p < 0.01$.**

from the low- to the high-dose periods for either systolic or diastolic values.

**Elderly group:** The average whole-day systolic BP significantly decreased from the control to the low-dose periods ($p < 0.05$) and to the high-dose period ($p < 0.05$). Average whole-day diastolic BP also showed significant decreases between the control and low- or high-dose periods. A further significant reduction in systolic BP was observed from the low- to the high-dose periods ($p < 0.01$), but this decrease was not seen in diastolic BP. Pulse rate did not change significantly among any of the 3 periods.

Although the average daytime systolic BP significantly decreased from the control to the low- and high-dose periods, no significant difference was observed between the low- and high-dose periods. However, average nighttime systolic BP showed a further reduction from the low- to the high-dose periods ($p < 0.01$), but diastolic BP showed no further reduction from the low- to the high-dose periods.

## DISCUSSION

The present study compared BP-lowering effects of low- and high-dose nifedipine tablets over 24 hours between older and younger hypertensive patients. A similar reduction of average whole-day BP was observed at low doses of nifedipine tablets (10 mg twice daily) in both younger and older groups. However, administration of high doses (20 mg twice daily) led to a further reduction in the 24-hour average of systolic BP in the elderly group only, with no further reduction in the younger group. Separate analysis of the whole-day BP into daytime and nighttime values revealed that this further reduction of systolic BP after the administration of a high dose seen only in the elderly group was mainly a reflection of a nighttime decrease.

There are 3 possible explanations for further reduction of BP after administration of the high dose in the elderly group: First, age-related pharmacokinetic changes due to a decreased rate of hepatic metabolism with aging may cause a larger BP reduction in the elderly because of high concentration and prolonged half-lives of antihypertensive agents.[5-7] We have previously reported greater maximal concentration and half-life time of nifedipine, associated with a larger reduction of BP in elderly hypertensive patients, compared with results in younger hypertensive patients, even if patients had no overt hepatic or renal disease.[8]

Second, a diminished sensitivity of the arterial and cardiopulmonary baroreceptor reflex with aging[9-13] may bring about a further reduction in BP during the night after high-doses of nifedipine are given to elderly patients. Gribbin et al[12] noted that bradycardia accompanying an increase in BP, induced by intravenously injected phenylephrine, was reduced as the age of subjects increased. In agreement with their findings, pulse rate in our elderly group did not change from control to treatment 2, whereas a significant increase in pulse rate accompanied by a reduction in BP was observed in the younger group, suggesting a diminished baroreceptor reflex in the elderly group. Several animal[14,15] and human experiments[16,17] have demonstrated not only diminished sensitivity of the baroreceptor heart-rate reflex, but also a decrease of baroreceptor control of peripheral circulation and BP. Third, the pathogenetic difference of hypertension between elderly and younger patients may be involved in the different BP-reducing actions of nifedipine. In younger patients, hypertension is often associated with a hyperdynamic circulation, preserved renal function and normal vascular resistance. In elderly patients, in contrast, hypertension is often accompanied by decreased cardiac output, normal or low plasma volume, decreased renal function and increased vascular resistance.[18] Therefore, based on the hemodynamic profiles of hypertension in the elderly and the mechanisms of action of calcium antagonists, some investigators[19] insist that calcium antagonists are more suited to older patients rather than younger patients. It is feasible that the exaggerated BP-lowering effect with high doses of nifedipine in the elderly group was brought about by a combination of the aforementioned 3 mechanisms. Although it was not clear how a reduction in BP during the night influences the target organ damage and prognosis of the patients, caution should be paid to rapid overreduction of BP when doses of antihypertensive agents are increased in elderly hypertensive patients.

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# Effects of Hydrochlorothiazide, Diltiazem and Enalapril on Mononuclear Cell Sodium and Magnesium Levels in Systemic Hypertension

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**Sixteen patients (mean age 68 years) with mild to moderate hypertension were treated with either diltiazem or hydrochlorothiazide for 6 weeks, followed by enalapril for a further 6 weeks. A second group of 40 patients (mean age 71 years) was treated with either hydrochlorothiazide or enalapril for 12 weeks; nonresponders received both drugs for 8 weeks. Treatment with hydrochlorothiazide or enalapril resulted in a lowering of systolic and diastolic blood pressures, but diastolic pressure was lower in patients treated with enalapril (89 ± 2 and 82 ± 2 mm Hg, respectively; $p < 0.05$). Treatment with diltiazem resulted in a decrease in diastolic pressure only. Treatment with hydrochlorothiazide resulted in a 17% decrease in serum potassium ($p < 0.05$), which returned to normal when enalapril was substituted. Hydrochlorothiazide also produced a 23% decrease in mononuclear cell sodium content at 4 weeks ($p < 0.01$), with a further 15% decrease at 12 weeks ($p < 0.05$). Mononuclear cell potassium and magnesium also decreased at 12 weeks by 18 and 16%, respectively ($p < 0.05$). All these effects were reversed when enalapril was substituted. A similar pattern of events was seen with diltiazem, which was again reversed with enalapril. Finally, there was no relation between changes in mononuclear cell sodium or other cation content and changes in blood pressure.**

**(Am J Cardiol 1991;68:1357–1361)**

Prolonged diuretic therapy in hypertensive patients[1] and after myocardial infarction[2] reduces both and the potassium and magnesium contents in mononuclear cells. It is not clear whether there is a true physiologic relation between changes in intracellular electrolyte content and changes in blood pressure, or whether such changes are a response to other pharmacologic factors. We attempted to examine such relations in a clinically relevant situation by studying the time-related response to 3 pharmacologically different antihypertensive agents. In addition, we studied the effect of the newer agents on intracellular electrolyte content in elderly patients.

The purpose of this study was to: (1) compare the effects of a calcium antagonist (diltiazem), a converting enzyme inhibitor (enalapril) and a thiazide diuretic (hydrochlorothiazide) on the mononuclear cell content of electrolytes in elderly patients (aged ≥60) with mild to moderate hypertension; (2) determine whether treatment with enalapril, alone or in combination with hydrochlorothiazide, would reverse any changes in intracellular electrolyte content produced by either hydrochlorothiazide or diltiazem alone; and (3) determine what extent changes in blood pressure in response to single or combination therapy could be related to changes in intracellular electrolyte content.

## METHODS

Two separate studies were performed on 2 different groups of geriatric patients with mild to moderate essential hypertension. Exclusion criteria included: diastolic pressure ≥120 mm Hg; ongoing diuretic therapy for cardiac failure; contraindications for therapy with any 1 of the 3 drugs in question; unstable angina pectoris, or recent (1 month) history of myocardial infarction or stroke; and blood urea nitrogen ≥40 mg/dl. The studies were approved by the Hospital Helsinki Committee, and all patients gave written informed consent.

In both studies, all treatment with antihypertensive drugs, diuretics, calcium antagonists or converting enzyme inhibitors were stopped for a period of 2 weeks. Supine blood pressure was measured weekly in the same arm. Patients with diastolic pressure ≥95 mm Hg

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at the end of this period were included in the study. Venous blood was withdrawn for routine hematology and biochemistry. In particular, blood samples were obtained for the measurement of sodium, potassium, magnesium and calcium in both the serum and the mononuclear cell.[3] In the first study blood was withdrawn on entry, and again at 6 and 12 weeks; in the second study, on entry, and again at 4 and 12 weeks.

**Study protocol:** STUDY 1: Patients who met the admission criteria at the end of the washout period were computer-randomized in 2 groups to receive either hydrochlorothiazide or diltiazem for 6 weeks, the daily dose of the drug being titrated to achieve a diastolic pressure ≤90 mm Hg. Average daily dose of the 2 drugs was 25 and 240 mg, respectively. At the end of 6 weeks, all patients were treated with enalapril only for a further 6 weeks, again titrated to keep the diastolic pressure ≤90 mm Hg. Average daily dose was 10 mg.

STUDY 2: In this study patients who met the admission criteria at the end of the washout period were randomized into group A (hydrochlorothiazide) or B (enalapril). Treatment was initially for 4 weeks during which the daily dose of either drug was increased weekly to a maximum of 25 and 20 mg, respectively, aiming at achieving a diastolic blood pressure ≤90 mm Hg. Patients whose blood pressure did not reach this level at the end of 4 weeks were classified as "nonresponders" and formed a third group (C) to receive both enalapril (10 mg daily) and hydrochlorothiazide (12.5 mg). The treatments for both groups of "responders" (A and B) and for the group of nonresponders (C) were then continued for a further 8 weeks.

Statistical analysis was performed using Student's *t* test for paired and unpaired observations.

## RESULTS

**Study 1:** Sixteen patients constituted this study (8 patients per group). Mean age was 68 years (range 66 to 74) for patients in group 1 (hydrochlorothiazide), and 72 years (range 65 to 80) for group 2 (diltiazem).

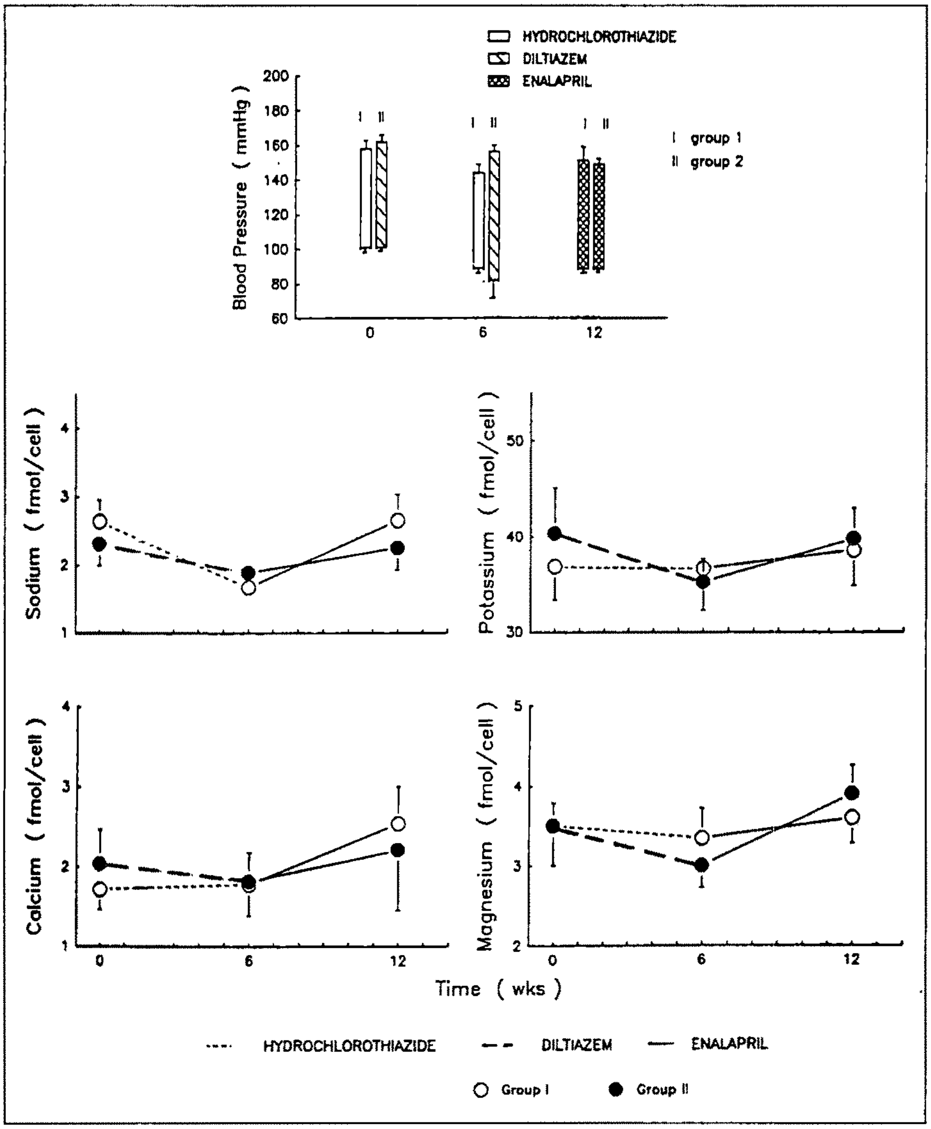

**FIGURE 1. Blood pressure and mononuclear cell cation levels in patients treated with either hydrochlorothiazide or diltiazem for 6 weeks, followed by enalapril for 6 weeks.**

**Study 2:** Forty patients constituted this study (19 in group A, 8 men and 11 women, average age 71 years [range 61 to 87], and 21 in group B, 11 men and 10 women, average age 73 years [range 63 to 85]). Thirteen patients (5 from group A and 8 from B, 3 men and 10 women, average age 70 years [range 61 to 84]) were nonresponders (C). Thus, 14 patients completed the study on hydrochlorothiazide, 13 on enalapril and 13 on both drugs.

**Effect on blood pressure:** STUDY 1: The effects on blood pressure are shown in Figure 1. Treatment with diltiazem resulted in a significant decrease in diastolic pressure only (162 ± 4/101 ± 2 to 156 ± 4/82 ± 10 mm Hg; $p < 0.05$), whereas systolic and diastolic pressures were reduced with hydrochlorothiazide (158 ± 5/101 ± 2 to 144 ± 5/89 ± 3 mm Hg; $p < 0.001$). When enalapril was substituted for these 2 drugs, systolic pressure in patients previously receiving diltiazem decreased significantly (156 ± 4 to 149 ± 3 mm Hg; $p < 0.05$) with no further change in diastolic pressure. There was no change in blood pressure in the group who had previously received hydrochlorothiazide.

STUDY 2: Blood pressure decreased in groups A (hydrochlorothiazide) and B (enalapril) after 4 weeks (184 ± 3/108 ± 2 to 156 ± 4/94 ± 2, and 190 ± 4/110 ± 1 to 163 ± 4/94 ± 2 mm Hg, respectively; $p < 0.001$) with no further decrease after 12 weeks (Figure 2). However, after 12 weeks, group B had a significantly lower diastolic pressure than A (82 ± 2 vs 89 ± 2 mm Hg; $p < 0.05$). Blood pressure decreased in group C (nonresponders) after 8 weeks of combined therapy (group A: 180 ± 3/98 ± 8 to 158 ± 5/92 ± 3 mm Hg; and group B: 181 ± 2/100 ± 4 to 163 ± 3/94 ± 2 mm Hg; $p < 0.001$).

**TABLE I** Mononuclear Cation Content (fmol/cell; mean ± SE) in 56 Patients with Mild to Moderate Hypertension and in 11 Control Subjects

| | Control Subjects | Pts. with Hypertension |
|---|---|---|
| Sodium | 3.33 ± 0.37 | 3.08 ± 0.17 |
| Potassium | 40.2 ± 3.7 | 42.7 ± 2.0 |
| Magnesium | 3.99 ± 0.33 | 3.90 ± 0.12 |
| Calcium | 3.22 ± 0.37* | 2.96 ± 0.13* |

*$p < 0.05$.
SE = standard error.

**Serum values:** STUDY 1: No changes were seen throughout the study in serum glucose, blood urea nitrogen, creatinine or cholesterol with either diltiazem or enalapril. At 6 weeks patients receiving hydrochlorothiazide had a 28% increase in serum uric acid ($p < 0.001$) that returned to normal when enalapril was substituted ($p < 0.005$). Serum potassium decreased by

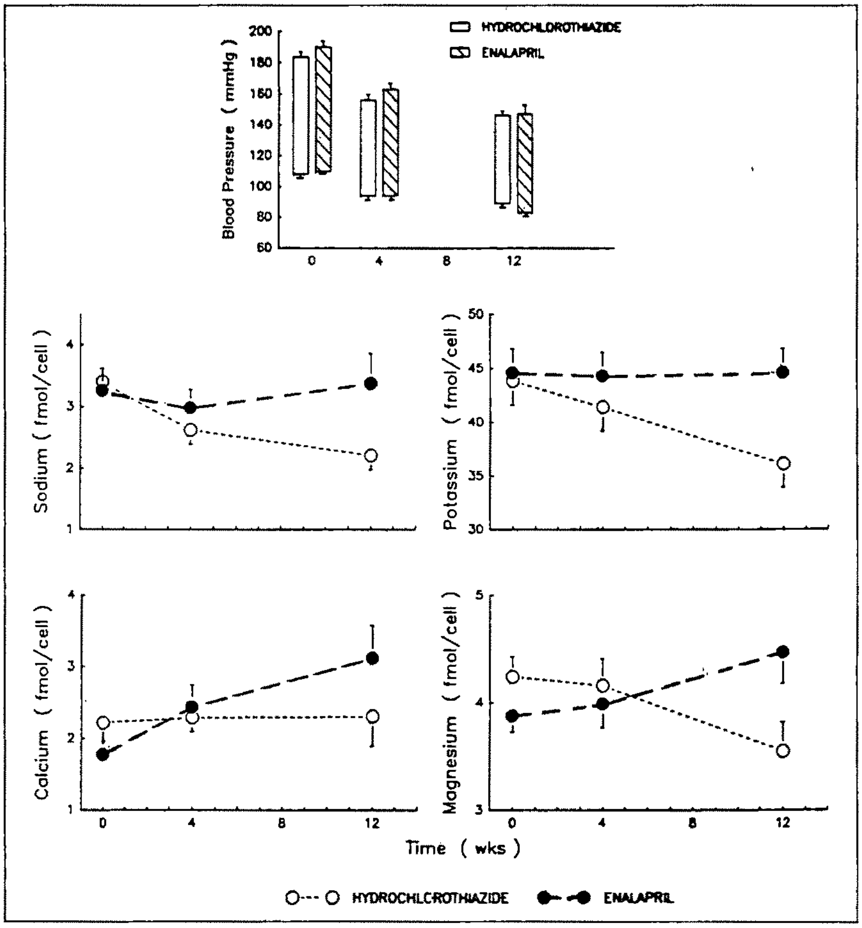

**FIGURE 2. Blood pressure and mononuclear cell cation levels in patients treated with either hydrochlorothiazide or enalapril for 12 weeks.**

17% ($p < 0.05$) after 6 weeks in patients receiving hydrochlorothiazide, and also returned to normal when enalapril was substituted ($p < 0.05$).

STUDY 2: Patients receiving hydrochlorothiazide for 12 weeks also had a 17% increase in serum uric acid ($p < 0.05$), whereas those with combined therapy did not. No changes in serum electrolytes were observed.

**Mononuclear cells:** Table I shows that there was no significant difference in the mononuclear cell content of sodium, potassium, magnesium or calcium between the 56 mild to moderate hypertensive patients before treatment and an age-matched group of 11 normotensive control subjects.

STUDY 1 (FIGURE 1): The mononuclear cell sodium content decreased by 37% in patients receiving hydrochlorothiazide ($p < 0.01$), returning to normal when enalapril was substituted. There was an 18% reduction in intracellular sodium in patients receiving diltiazem, but this was not statistically significant. There was also a trend for mononuclear cell potassium, magnesium or calcium to decrease during 6 weeks of therapy with hydrochlorothiazide or diltiazem; this was reversed with enalapril.

STUDY 2 (FIGURE 2): The mononuclear cell sodium content decreased by 23% at 4 weeks ($p < 0.01$) with a further 16% decrease at 12 weeks ($p < 0.05$). Similarly, both intracellular potassium and magnesium decreased at 12 weeks (18 and 16%, respectively; $p < 0.05$). Treatment with enalapril resulted in a 37% increase in intracellular calcium at 4 weeks ($p < 0.05$) with a further but nonsignificant increase at 12 weeks. Magnesium increased by 15% at 12 weeks ($p < 0.01$).

NONRESPONDERS (FIGURE 3): Patients receiving hydrochlorothiazide had a 26% reduction in mononuclear cell sodium content ($p < 0.06$). In combination with enalapril, this trend was reversed, and mononuclear cell po-

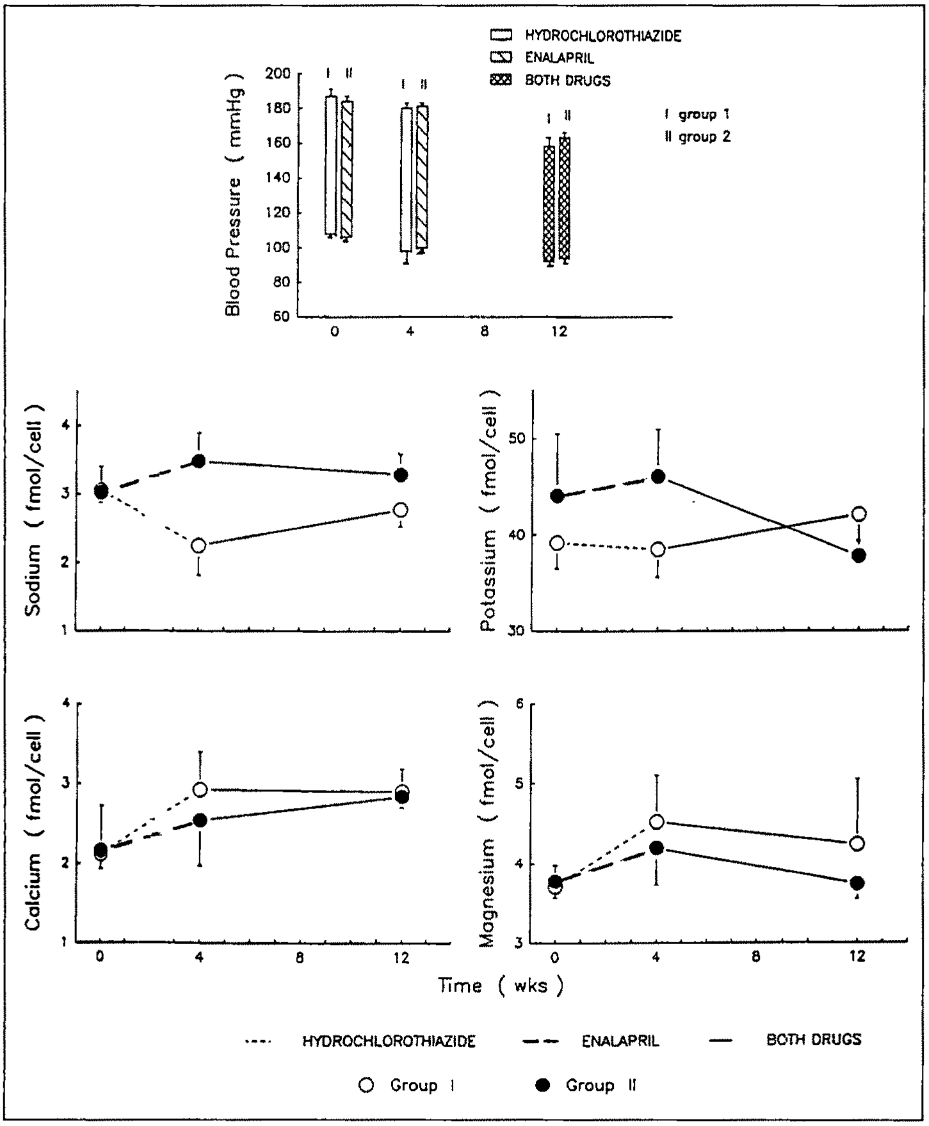

**FIGURE 3. Blood pressure and mononuclear cell cation levels in patients treated with either hydrochlorothiazide or enalapril for 4 weeks. Because blood pressure did not decrease, patients were then treated with a combination of both drugs for a further 8 weeks.**

tassium content was also increased. Opposite trends were seen in patients who received enalapril before hydrochlorothiazide.

## DISCUSSION

Patients with severe heart failure treated with enalapril for 12 weeks have no change in their mononuclear cell cation content,[4] and Enalapril also reverses hydrochlorothiazide-induced hypokalemia.[5,6] The present study shows that treatment with enalapril reverses the hydrochlorothiazide-induced loss of intracellular cations. This is true whether Enalapril was substituted for (Figure 1) or combined with (Figure 3) hydrochlorothiazide. In a preliminary study Malini et al[7] showed that a combination of enalapril and a thiazide diuretic prevents the reduction in mononuclear cell magnesium content seen with the thiazide diuretic alone.

Our study also shows that enalapril alone or in combination with a diuretic can produce adequate reduction of blood pressure without affecting intracellular cation content. Most striking is the reversal of the thiazide-induced decrease in intracellular sodium content by enalapril (Figure 1) with no concomitant increase in blood pressure. Furthermore, no consistent relation was found between changes in intracellular cation content and blood pressure. Araoye et al[8] have also shown that decreasing blood pressure does not affect intracellular cation content. Therefore, it is difficult to explain the changes in intracellular content as either a cause or an effect of changes in blood pressure.

It has been suggested that elderly hypertensive patients are less sensitive to converting enzyme inhibitors.[9] The results of both our studies show that in an elderly group of mild to moderate hypertensive patients, all 3 drugs were successful in reducing blood pressure, with >75% of these patients requiring only single drug therapy. All 3 drugs were well-tolerated with no side effects. In particular, the effect of combined therapy with enalapril and hydrochlorothiazide produced a significant reduction in blood pressure without any adverse effects on intracellular cation content.

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# Response to Mental and Physical Stress Before and During Adrenoreceptor Blocker and Angiotensin-Converting Enzyme Inhibitor Treatment in Essential Hypertension

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**The effects of mental, static and dynamic stresses on physiologic parameters before and after β-blocker (n = 24) and angiotensin-converting enzyme inhibitor (n = 29) treatment were examined. Mental stress induced similar elevation in systolic and diastolic blood pressures (BPs) with and without β-blocker treatment. During angiotensin-converting enzyme inhibitor treatment, the change in systolic BP was significantly greater ($p < 0.05$). Heart rate response was attenuated by β blockers and unchanged by the angiotensin-converting enzyme inhibitor. Skin temperature and galvanic skin resistance significantly decreased ($p < 0.05$) with mental stress. Beta blockers did not change the response pattern, whereas the angiotensin-converting enzyme inhibitor attenuated the stress-induced reduction of both skin temperature and galvanic skin response. After handgrip exercise, increases in systolic and diastolic BPs and heart rate were similar before and after β-blocker treatment, whereas the angiotensin-converting enzyme inhibitor induced small but significantly fewer ($p < 0.05$) changes in diastolic BP and heart rate. Treadmill exercise induced similar changes in systolic and diastolic BPs with both treatments compared with no treatment. The angiotensin-converting enzyme inhibitor appears to provide additional protection to that seen with β blockers during mental and static stressors by blunted changes in skin temperature and galvanic skin resistance.**

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Blood pressure (BP) and heart rate change during the day in response to mental and physical activity.[1,2] This change is exaggerated in hypertensive populations.[3-6] The partial contribution of mental or physical stress to average BP levels[4-7] varies according to socioeconomic, ethnic, cultural and personal factors. Development of persistent hypertension as a consequence of stressful stimuli is still a matter of controversy.[7,8]

Many studies have attempted to evaluate the hemodynamic effect of psychological and physical stressors in a systematic fashion in the laboratory.[9-12] Some concentrated on the patterns of response; others on the magnitude of change of the different parameters. It is not yet clear whether the responses to psychological or physical stressors in research settings correlate with the responses encountered in real life situations.[12,13] Some investigators believe that cardiovascular reactivity may predict future development of hypertension in normotensive high-risk subjects,[14-16] whereas others are unable to observe such predictive value.[17] Response patterns to simulated stressors in treated hypertensive patients are even more obscure and difficult to interpret.[18] It is accepted that antihypertensive agents should reduce BP not only at rest but also during exposure to stress. There are few studies on the response pattern of physiologic parameters to experimental psychological stress and how this response is modified by different antihypertensive medications. Therefore, we decided to pool data obtained in our laboratory during the last 3 years on patients before and after treatment with 4 different β-adrenergic blocking drugs and 1 angiotensin-converting enzyme inhibitor.

## METHODS

**Subjects:** Fifty-three men (age range 25 to 50 years) with mild hypertension were selected from the Outpatient Hypertension Clinic at the Soroka Medical Center. Hypertension was diagnosed if sitting cuff readings of $\geq$140/95 mm Hg (Korotkoff phase v) were obtained on $\geq$3 separate visits, 2 weeks after discontinuation of any antihypertensive medication. Secondary hypertension was excluded by routine investigation, as

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**TABLE I** Effect of Mental Stress on Various Parameters Before and After Antihypertensive Treatments (mean levels)

| | No Treatment | | | Beta Blockers | | | Angiotensin-Converting Enzyme Inhibitor | | |
|---|---|---|---|---|---|---|---|---|---|
| Parameters | BL | Max. | Δ | BL | Max. | Δ | BL | Max. | Δ |
| Systolic BP (mm Hg) | 147 | 160 | 13 | 126 | 138 | 12 | 136 | 155 | 19 |
| Diastolic BP (mm Hg) | 94 | 109 | 15 | 82 | 98 | 16 | 92 | 103 | 11 |
| Heart rate | 72 | 82 | 10 | 67 | 71 | 4† | 74 | 85 | 11 |
| Temp. (°C) | 29.1 | 28.1 | −1.0 | 31.2 | 29.9 | −1.3 | 30.5 | 30.1 | −0.4* |
| GSR decrease (%) | — | — | 40 | — | — | 33 | — | — | 21* |

*$p < 0.05$ compared with no treatment and with β blockers.
†$p < 0.05$ compared with no treatment and with angiotensin-converting enzyme inhibitor.
Systolic and diastolic blood pressures and heart rate increased significantly ($p < 0.05$) from baseline to maximal values in each treatment group.
BL = baseline; BP = blood pressure; GSR = galvanic skin resistance; Max. = maximal value; Temp. = temperature; Δ = maximal value-baseline.

well as target organ involvement. Informed written consent was obtained from each patient and the protocol was approved by the Hospital's Ethics Committee.

**Protocol:** Each patient started a 2-week, single-blind, placebo washout treatment. During this period he was evaluated on 3 separate visits. The diagnosis of hypertension was established. Full medical history, complete physical examination, laboratory test, electrocardiography and chest x-ray were performed. The "β blocker group" (24 patients) at the end of the washout period entered a double-blind treatment with 1 of the following drugs: bopindolol (1 mg), atenolol (50 mg), labetalol (400 mg) or propranolol (160 mg) for 2 weeks. A 2-week, single-blind, second washout period followed; then, a different β blocking drug was administered in double blind manner for 2 additional weeks. The angiotensin-converting enzyme inhibitor group (29 patients) was treated with enalapril (20 mg) for 4 weeks. On the last day of the washout period, and on the last day of each drug period, the patient underwent the following 3.5-hour evaluation. The patient arrived at the laboratory after consuming a light breakfast free of tea, coffee or cigarettes. After 30 minutes of rest a sitting baseline was obtained: BP and heart rate were measured. After the baseline evaluation, the response to psychological stress was examined by a mental arithmetic test.[15] The patient performed sequential subtraction of a 2-digit number from a 4-digit number. He was urged to perform as best as he could. Every minute a new exercise was started and the end of each minute was marked by a loud clock ring. The difficulty of the test was adjusted according to each subjects' background. This test lasted for 5 minutes, and was followed by a 10-minute relaxation period. During each minute of the test and twice during the relaxation, BP and heart rate were measured. Galvanic skin resistance[19] and peripheral skin temperature were continuously recorded with the aid of a specially developed physiologic processor (Atlas Research Industries). After 30 minutes of rest, a static handgrip exercise was performed in the sitting position. Maximal voluntary static contraction was determined 10 minutes before the test. The average contraction was calculated from 2 consecutive maximal handgrip attempts. The subjects performed a sustained 50% of the maximal voluntary contraction for 3 minutes. BP and heart rate were measured every minute. After 30 minutes of rest, a treadmill exercise test was performed according to the modified Bruce protocol. The electrocardiogram was monitored continuously, and BP and heart rate were recorded every 2 minutes. The test was terminated when the patient reached maximal capacity, or maximal allowed heart rate, or if he stopped the exercise for any other reason.

The SPSS program was used for paired comparisons of mean values (Student's $t$ test). Analysis of variance for crossover designs was applied to ensure the lack of effect of the treatment administration sequence on our results.

## RESULTS

Despite the differences in the mechanism of action of the 4 β blockers, the patterns of findings for each treatment were similar. Therefore the final results were aggregated and presented as the mean of 1 β-blocker treatment group. Furthermore, these results were compared with those of the angiotensin-converting enzyme inhibitor treatment group.

Table I lists baseline and maximal values of the various parameters during the mental stress test. The effect of mental stress was evaluated before and after the 2 antihypertensive treatments. Both treatment regimens reduced baseline systolic BP significantly ($p < 0.05$), although β blockers reduced it more than the angiotensin-converting enzyme inhibitor ($p < 0.05$). The baseline diastolic BP was significantly ($p < 0.05$) reduced by β blockers only. Systolic and diastolic BPs and heart rate increased significantly ($p < 0.05$) from baseline to maximum after mental stimuli, and before and after each of the 2 treatment regimens. The change (Δ) in systolic BP (baseline to maximum) was similar before

**TABLE II** Effect of Handgrip Exercise on Blood Pressure and Heart Rate Before and After Antihypertensive Treatments (mean levels)

| | No Treatment | | | Beta Blockers | | | Angiotensin-Converting Enzyme Inhibitor | | |
|---|---|---|---|---|---|---|---|---|---|
| Parameters | BL | Max. | Δ | BL | Max. | Δ | BL | Max. | Δ |
| Systolic BP (mm Hg) | 148 | 175 | 27 | 130 | 153 | 23 | 141 | 166 | 25 |
| Diastolic BP (mm Hg) | 98 | 119 | 21 | 86 | 105 | 19 | 92 | 99 | 7* |
| Heart rate | 76 | 94 | 18 | 66 | 82 | 16 | 79 | 90 | 11* |

*p <0.05 compared with no treatment and with β blockers.
Systolic and diastolic blood pressures and heart rate increased significantly (p <0.05) from baseline to maximal values in each treatment group.
Abbreviations as in Table I.

**TABLE III** Effect of Treadmill Exercise on Blood Pressure and Heart Rate Before and After Antihypertensive Treatments (mean levels)

| | No Treatment | | | Beta Blockers | | | Angiotensin-Converting Enzyme Inhibitor | | |
|---|---|---|---|---|---|---|---|---|---|
| | BL | Max. | Δ | BL | Max. | Δ | BL | Max. | Δ |
| Systolic BP (mm Hg) | 149 | 185 | 36 | 128 | 160 | 32 | 136 | 177 | 41 |
| Diastolic BP (mm Hg) | 97 | 102 | 5 | 88 | 94 | 6 | 92 | 99 | 7 |
| Heart rate | 79 | 177 | 98 | 67 | 131 | 64* | 98 | 183 | 85 |

*p <0.05 compared with no treatment and with angiotensin-converting enzyme inhibitor
Systolic and diastolic blood pressures and heart rate increased significantly (p <0.05) from baseline to maximal values in each treatment group.
Abbreviations as in Table I.

and during β-blocker treatment and significantly (p <0.05) higher with the angiotensin-converting enzyme inhibitor. Maximal systolic BP level was significantly (p <0.05) reduced by β blockers only. Maximal diastolic BP decreased with both treatments (p <0.05). Increases from baseline to maximal (Δ) levels did not differ significantly. Both baseline and maximal heart rate values were significantly reduced with β blockers only (p <0.05). Beta blockers also decreased the effect of the mental test on heart rate. Baseline and maximal levels of peripheral skin temperature (Table I) were higher during both treatment periods than without treatment (p <0.05). Mental stress induced a significant decrease in skin temperature before and during β-blocker treatment (p <0.05). No significant decrease was recorded after treatment with an angiotensin-converting enzyme inhibitor. The relative changes of galvanic skin response from baseline to maximal levels are listed in Table I. The greatest change occurred before treatment. Both treatments reduced this change, but angiotensin-converting enzyme inhibitors produced more of a change than β blockers (p <0.05).

Table II summarizes the effect of handgrip exercise test on BP and heart rate. Baseline and maximal systolic BP levels were significantly reduced with both treatments (p <0.05). However, the changes from baseline remained similar. Baseline and maximal diastolic BP levels were also significantly decreased with both treatments (p <0.05). During treatment with the angiotensin-converting enzyme inhibitor, a significantly (p < 0.05) smaller change from baseline (Δ) was observed compared with β blockers and no treatment. Beta blockers significantly reduced both baseline and peak levels of heart rate (p <0.05). However, the change from baseline to maximal (Δ) levels was significantly less during treatment with angiotensin-converting enzyme inhibitor (p <0.05).

The effects of treadmill exercise test on systolic and diastolic BPs and heart rate are listed in Table III. Baseline and maximal levels of systolic and diastolic BPs were significantly (p <0.05) reduced with both treatments. However, changes from baseline to maximal levels remained similar during the period without treatment as well as during both treatments. Baseline heart rate significantly increased (p = 0.05) with angiotensin-converting enzyme inhibitor therapy. Maximal heart rate significantly decreased (p <0.001) during β-blocker treatment. The lowest change in heart rate from baseline to maximal levels was observed with β-blocker treatment (p <0.05).

## DISCUSSION

The impact of everyday life stress on the sympathetic nervous system can be simulated and assessed in the laboratory by way of mental and physical stress tests. Our results confirm this hypothesis because all the physiologic parameters changed significantly from baseline under each stimulus. The variability in the responses of all subjects was low. Beta blockers and the angiotensin-converting enzyme inhibitor significantly reduced systolic and diastolic BPs at rest. Heart rate was reduced by β blockers only.

Mental stress induced an elevation in systolic and diastolic BPs with and without β-blocker treatment, as previously reported by Eliasson et al.[20] In both studies, the different β blockers produced similar results. During angiotensin-converting enzyme inhibitor treatment, the absolute change in systolic BP was significantly higher, whereas in diastolic BP it was lower. Heart rate reactivity was attenuated with β blocker therapy, and unchanged with angiotensin-converting enzyme inhibitor. Very similar patterns of response were reported in other studies.[18,20-23] Falkner et al[24,25] showed blunted BP and heart rate responses with metoprolol and clonidine, but not with hydrochlorothiazide in adolescent hypertensive patients.

The present study evaluated 2 additional indicators of mental stress: skin temperature and galvanic skin resistance. Both parameters were significantly affected by mental stress: skin temperature decreases, probably by adrenergic-receptor induced vasoconstriction in superficial vessels of the skin. Galvanic skin response changes in the same direction and this change is related to increased perspiration, although the underlying mechanism is not well understood. Divergent effects of $\beta$ blockers and angiotensin-converting enzyme inhibitor treatments on these parameters were observed. Beta blockers did not change the response pattern compared with no treatment, whereas the angiotensin-converting enzyme inhibitor attenuated the stress-induced reduction of both skin temperature and galvanic skin response.

Handgrip exercise induced significant increases in both BP and heart rate. Beta-blocker treatment, while reducing baseline and peak levels, did not block the pressor response to static exercise, since the absolute increments of systolic and diastolic BPs and heart rate were similar before and after treatment. Similar findings were reported with central and peripheral $\alpha$-receptor blocking drugs as well as with $\beta$ blockers.[26,27] On the other hand, enalapril significantly reduced changes in diastolic BP and heart rate. McInnes et al[23] report similar findings with calcium antagonist treatment. However, in studies of normotensive subjects, no change was found in the response to static stimulus after angiotensin-converting enzyme inhibitor administration or nifedipine treatment.[28,29]

During treadmill exercise both $\beta$-blocker and angiotensin-converting enzyme inhibitor treatments reduced baseline and maximal systolic and diastolic BPs. However, the exercise-induced absolute changes remained similar with both treatments compared with no treatment. Beta-blocker treatment significantly reduced baseline, maximal heart rate and its change from baseline compared with no treatment. Other studies report similar findings regarding $\beta$ blockers.[20,24,27] After angiotensin-converting enzyme inhibitor treatment, resting and maximal systolic BP levels decreased, whereas diastolic BP levels were not significantly reduced, and resting and maximal heart rate were slightly elevated. Different studies on angiotensin-converting enzyme inhibitors report conflicting findings.[28,30,31]

Active hypertensive patients are endangered not only by elevated BP at rest, but also by its frequent elevations due to everyday stressful situations. Thus, the aim of any antihypertensive treatment is to attenuate this risk. In our study, both $\beta$ blockers and an angiotensin-converting enzyme inhibitor provided considerable protection during rest and peak exercise. The absolute change (from baseline to maximum) under all stressful stimuli was unaffected by $\beta$-blocker treatment. However, the angiotensin-converting enzyme inhibitor treatment attenuated some of these changes. The main effect of a angiotensin-converting enzyme inhibitor is to reduce total peripheral resistance. Therefore, during static exercise — a powerful stimulus for the elevation of total peripheral resistance — the angiotensin-converting enzyme inhibitor indeed reduced the change in diastolic BP and in heart rate. The clinical significance of the modified response in skin temperature and galvanic skin response by the angiotensin-converting enzyme inhibitor has not yet been elucidated, but may be related to a more substantial blocking of angiotensin II than occurs with $\beta$ blockade. Because both parameters are sensitive indicators of mental stress, the attenuation of the response by angiotensin-converting enzyme inhibitors is possibly beneficial for the patient.

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# Clinical and Anatomic Observations in Patients Having Mitral Valve Replacement for *Mitral Stenosis* and Simultaneous Tricuspid Valve Replacement

Erik A. Eways, BS,* and William C. Roberts, MD

**Certain clinical and morphologic findings are described in 67 patients (aged 23 to 76 years [mean 52]; 55 women [82%]) who had mitral valve replacement for mitral stenosis (with or without associated regurgitation), and simultaneous tricuspid valve replacement for pure tricuspid regurgitation (58 patients) or tricuspid stenosis (all with associated regurgitation; 9 patients). Of the 58 patients with pure tricuspid regurgitation, 21 had anatomically normal and 37 had anatomically abnormal (diffusely fibrotic leaflets) tricuspid valves. Among these 58 patients, no clinical or hemodynamic variable was useful before surgery in distinguishing the group without from that with anatomically abnormal tricuspid valves. All 9 patients with stenotic tricuspid valves had anatomically abnormal tricuspid valves. The latter group had a lower average right ventricular systolic pressure (tricuspid valve closing pressure) than those with pure tricuspid regurgitation, and none had severe pulmonary arterial hypertension (present in 20 [30%] of the 58 patients with pure tricuspid regurgitation).**

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A significant percentage of patients with primary mitral valve disease have tricuspid valve dysfunction. Consequently, some patients undergoing mitral valve replacement or repair operations for primary mitral disease also have tricuspid valve replacement or other operative procedures performed on the right-sided atrioventricular valve. Among surgeons who perform many cardiac valve operations yearly, some rarely replace the tricuspid valve and others do so relatively frequently. If the tricuspid valve is stenotic, the decision is relatively easy; if it is purely regurgitant, the decision is more difficult. In the latter circumstance, the tricuspid valve leaflets may be anatomically abnormal, normal or virtually normal. In this report we focus on the frequency and type of structural abnormality of the tricuspid valve in patients having simultaneous replacement of both mitral and tricuspid valves for *mitral stenosis* and tricuspid valve dysfunction (either pure regurgitation or stenosis [with or without regurgitation]).

## METHODS

**Patients studied:** In the Surgery Branch of the National Heart, Lung, and Blood Institute from September 1963 to December 1989, a total of 113 patients >20 years of age underwent simultaneous replacement of the native mitral and tricuspid valves without aortic valve replacement at any time. Of the 113 patients, 11 were excluded from further analysis because a peak systolic pressure gradient between the left ventricle and a systemic artery >10 mm Hg was present. Another 18 patients were excluded because either the operatively excised tricuspid and mitral valves were not available for reexamination or photographs of these operatively excised valves were unavailable. Of the remaining 84 patients, 67 had mitral stenosis and 17 had pure mitral regurgitation. This report focuses on the 67 patients with mitral stenosis. Thirty-two (48%) of the 67 patients previously had valvular commissurotomy operations: mitral valve only (28 patients), tricuspid valve only (2), and both mitral and tricuspid valve commissurotomy (2). None of the 67 patients had a previous anuloplasty procedure on either the tricuspid or mitral valve.

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**TABLE I** Clinical, Hemodynamic and Anatomic Observations in 67 Patients Having Combined Mitral and Tricuspid Valve Replacement for Mitral and Tricuspid Valve Stenoses or Regurgitation, or Both

| | | | | | | | Pressures (mm Hg) | | | | | | | | | Dead After VR | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Right Atrium | | PAW or LA | | | | | | | | | | |
| Group | Type of Valve Dysfunction | Valve Anatomically Abnormal | No. of Pts. (%) | Age (yrs) at VR Range (mean) | Women (%) | Men (%) | Mean | V Wave | Mean | V Wave | RV (s/d) Average | LV (s/d) Average | RVSP ≤40 (%) | RVSP >70 (%) | LVSP >140 (%) | ≤60 Days (%) | 12 Mos | 60 Mos | 10 Yrs |
| 1 | MS,TR | MV | 21 (31) | 23–75 (54) | 17 (81) | 4 (19) | 12 | 21 | 22 | 29 | 61/11 | 117/12 | 5 (24) | 4 (19) | 2 (10) | 2/21 (10) | 4/19 | 8/17 | 11/16 |
| 2 | MS,TR | MV & TV | 37 (55) | 25–76 (54) | 29 (78) | 8 (22) | 14 | 22 | 26 | 35 | 68/13 | 117/14 | 7 (19) | 16 (43) | 3 (8) | 8/37 (22) | 8/34 | 10/29 | 15/23 |
| 3 | MS,TS | MV & TV | 9 (14) | 29–55 (40) | 9 (100) | 0 (0) | 13 | 20 | 19 | 32 | 47/10 | 121/13 | 2 (22) | 0 (0) | 2 (22) | 2/9 (22) | 3/9 | 3/9 | 3/6 |
| Totals or means | | | 67 (100) | 23–76 (52) | 55 (82) | 12 (18) | 13 | 21 | 23 | 33 | 63/12 | 118/13 | 14 (21) | 20 (30) | 7 (10) | 12/67 (18) | 5/62 (24%) | 21/55 (38%) | 29/45 (64%) |

LA = left atrium; LV = left ventricle; LVSP = left ventricular peak systolic pressure; MS = mitral stenosis (with or without mitral regurgitation); MV = mitral valve; PAW = pulmonary artery wedge; RV = right ventricle; RVSP = right ventricular peak systolic pressure; s/d = peak systole/end-diastole; TR = tricuspid regurgitation; TS = tricuspid stenosis; TV = tricuspid valve; VR = valve replacement.

**Year of operation and surgeon:** The 67 valve replacement operations were performed by 6 different surgeons during the following time periods: 1963 to 1965 (1 patient); 1966 to 1970 (13); 1971 to 1975 (20); 1976 to 1980 (16); 1981 to 1985 (10); and 1986 to 1989 (7).

**Classifications and definitions:** The clinical records of all 67 patients were reviewed. The operatively excised valves had all been examined and classified initially by WCR. Of the 134 operatively excised valves in the 67 patients, 62 were reexamined, and photographs of the other 72 were examined. The original description of the operatively excised valve by WCR was reviewed in all 67 patients.

The patients were divided into 3 groups on the basis of valvular function and structure (Table I). The leaflets in all stenotic valves (both mitral and tricuspid) were diffusely fibrotic, and the mitral leaflets were often focally calcified. Calcific deposits were absent in all stenotic tricuspid valves. Nonstenotic, purely regurgitant tricuspid valves considered anatomically abnormal were also diffusely fibrotic, but their orifices were nonstenotic. Tricuspid valves considered anatomically normal were free of diffuse leaflet or chordal thickening; some had small focal leaflet thickenings involving 1 or 2 leaflets. (These focal thickenings were considered consequences of increased right ventricular systolic or closing pressure on the leaflets.) All patients with mitral stenosis were considered to have rheumatic heart disease. Mitral and tricuspid stenoses were confirmed in all patients by cardiac catheterization before surgery. All 67 patients had right- and left-sided cardiac catheterization during the 6 weeks preceding simultaneous replacement of the native mitral and tricuspid valves.

## RESULTS

Certain clinical, hemodynamic and morphologic findings in the 67 patients (55 women [82%]) are listed in Table I, and some valves are illustrated in Figures 1 to 5. Of the 67 patients, 9 (14%) had associated tricuspid valve stenosis (group 3) and, consequently, anatomically abnormal tricuspid valves; 58 (86%) had pure tricuspid valve regurgitation, 21 (31%) with anatomically normal (group 1) and 37 (55%) with anatomically abnormal tricuspid valves (group 2). No significant differences among the 3 groups were observed before surgery in mean right atrial pressure, average right atrial peak V wave, percentage of patients with peak right ventricular systolic pressure ≤40 mm Hg, peak left ventricular systolic pressure, percentage of patients with peak left ventricular systolic pressure >140 mm Hg, average peak systemic arterial systolic pressure, and mean and average V wave in the pulmonary artery wedge position or left atrium. Patients in group 3 (mitral and tricuspid stenoses) had lower average peak right ventricular systolic pressure and percentage of patients with right ventricular systolic pressures >70 mm Hg than those in the other 2 groups had.

## DISCUSSION

The present study focuses on structural alterations in operatively excised tricuspid valves in patients having mitral valve replacement because of mitral stenosis. Pa-

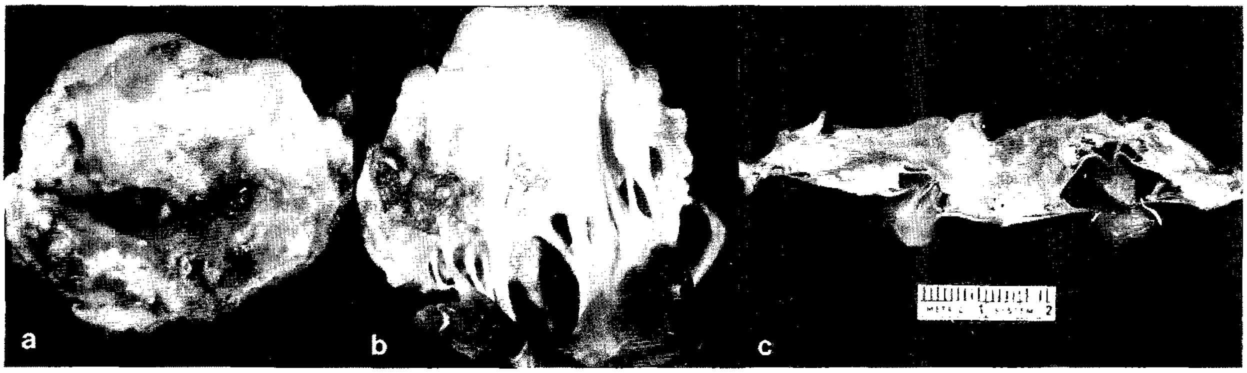

**FIGURE 1. Operatively excised stenotic mitral valve *(a* and *b)*, and purely regurgitant and anatomically normal tricuspid valve *(c)* in 59-year-old woman (S74-5134). Mean diastolic gradient across mitral valve was 18 mm Hg. Right ventricular pressure was 50/7 mm Hg, and left ventricular pressure was 124/9 mm Hg.**

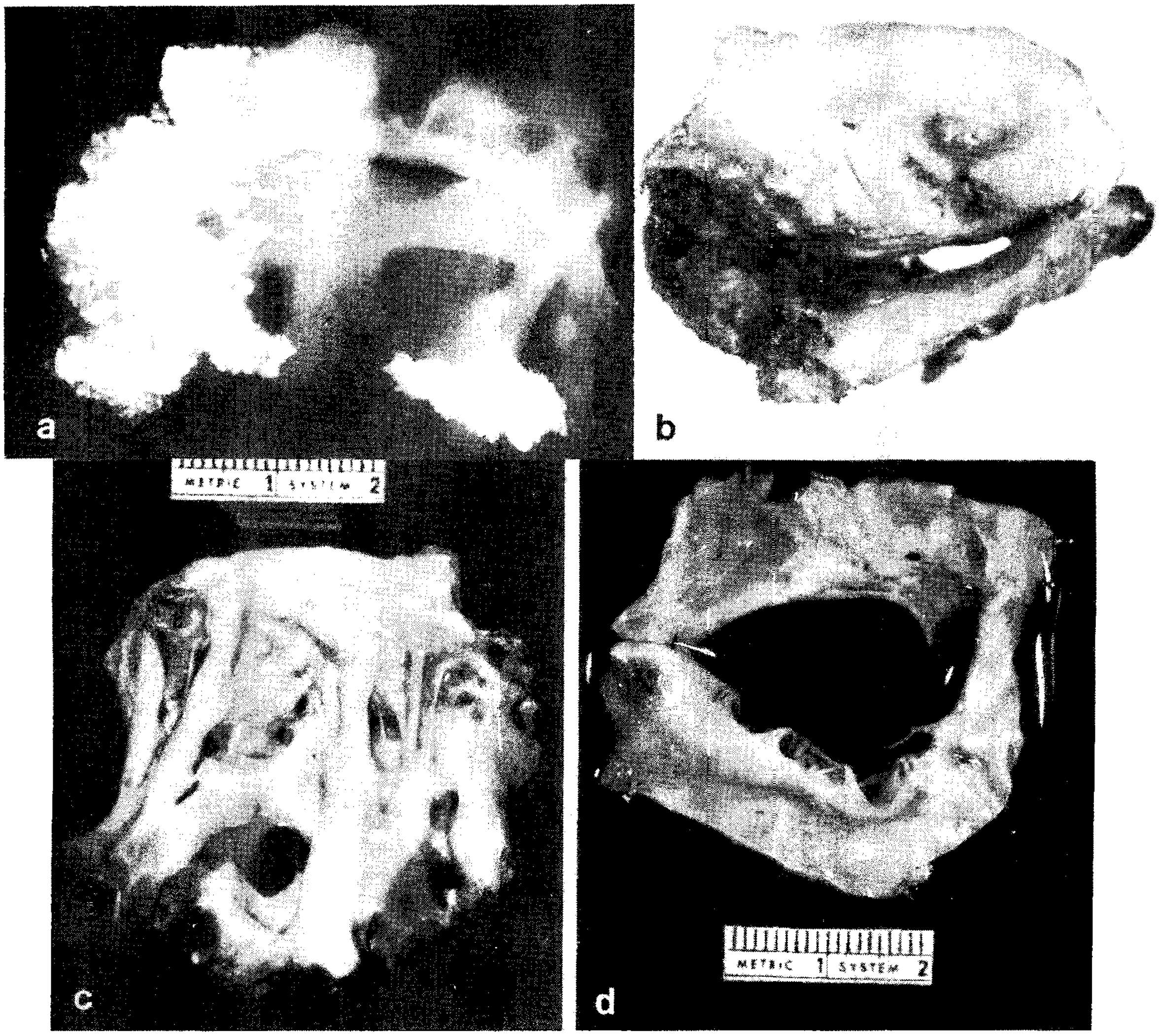

**FIGURE 2. Operatively excised stenotic mitral valve *(a* to *c)* and purely regurgitant, diffusely fibrotic tricuspid valve *(d)* in 65-year-old man (S74-5046). Right ventricular pressure was 120/27 mm Hg, and left ventricular pressure was 100/25 mm Hg. The mitral valve is calcified.**

tients whose indication for mitral valve replacement was pure mitral regurgitation were excluded from this study. Of the 67 patients having stenotic mitral valves replaced, the leaflets and chordae tendineae of all mitral valves were diffusely fibrotic with or without calcific deposits.[1,2] The operatively excised tricuspid valves in these patients were anatomically normal in 21 patients (31%) and anatomically abnormal (diffusely fibrotic) in 46 (69%). The tricuspid valves in the latter 46 patients were purely regurgitant in 37 (80%) and stenotic

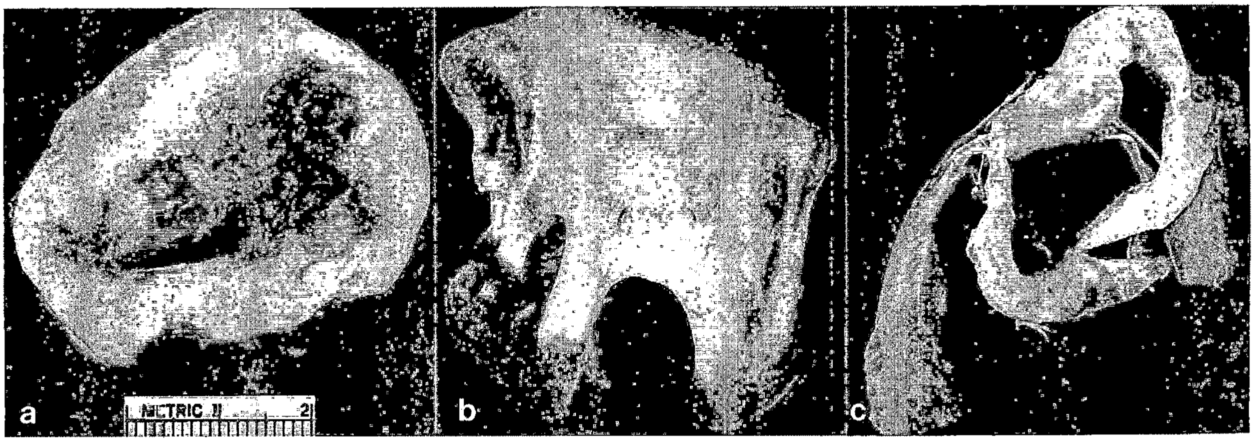

**FIGURE 3.** Operatively excised stenotic mitral valve *(a* and *b)* and diffusely fibrotic purely regurgitant tricuspid valve *(c)* in 54-year-old man (S58-2439). Right ventricular pressure was 65/10 mm Hg, and left ventricular pressure was 110/12 mm Hg.

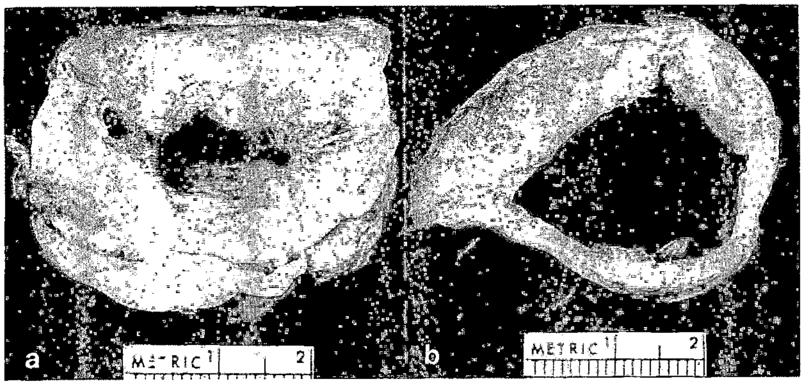

**FIGURE 4.** Operatively excised stenotic mitral valve *(a)* and diffusely fibrotic mildly stenotic tricuspid valve *(b)* in 55-year-old woman (S71-3034). Right ventricular pressure was 38/11 mm Hg, and left ventricular pressure was 148/14 mm Hg.

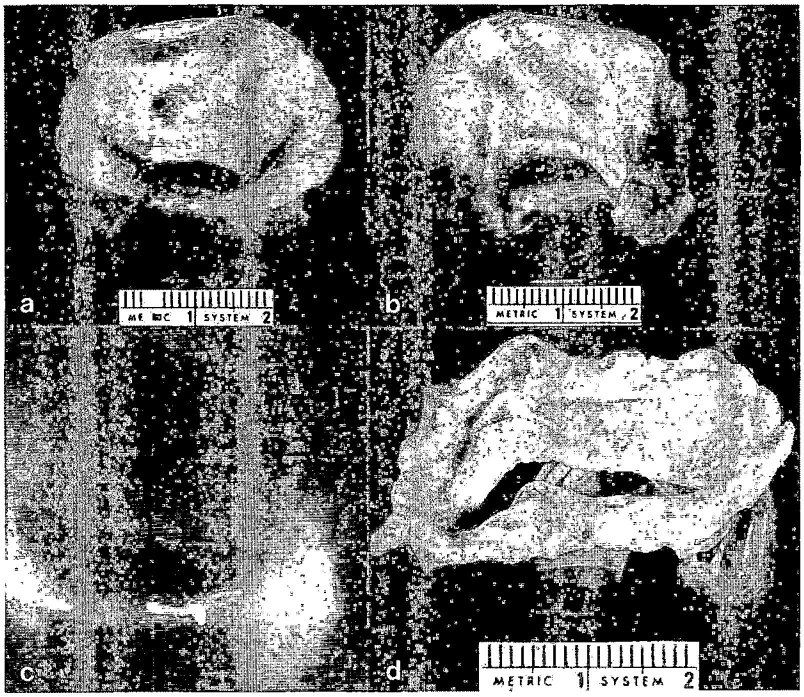

**FIGURE 5.** Operatively excised stenotic mitral valve *(a* to *c)* and stenotic tricuspid valve *(d)* in 29-year-old woman (S74-5057) whose right ventricular pressure was 45/15 mm Hg and whose left ventricular pressure was 110/18 mm Hg. Radiograph *(c)* shows only small deposit of calcium in 1 mitral leaflet.

(mean right atrial to right ventricular mean diastolic gradient ranged from 3 to 11 mm Hg [average = 6]) with or without associated regurgitation in 9 (20%).

When a cardiac valve (tricuspid or any other cardiac valve) is stenotic, the valve leaflets are diffusely fibrotic or extensively calcified (i.e., anatomically abnormal).[2,3] Among patients with mitral stenosis severe enough to warrant a mitral valve operation, associated tricuspid valve stenosis is infrequent (14% in the present study). This percentage, however, is much less if the analysis does not focus exclusively on patients having simultaneous replacement of both the mitral and tricuspid valves. In the study by Roberts[2] focusing on necropsy patients with fatal valvular heart disease (some of whom had had cardiac operations and some of whom had not), 434 (43%) of 1,010 patients ≥15 years of age had mitral stenosis with or without associated mitral regurgitation. Of the 434 patients, mitral stenosis was not associated with aortic valve dysfunction or tricuspid stenosis in 189 (44%); it was combined with aortic stenosis in 152 (35%), with pure aortic regurgitation in 65 (13%), with both aortic and tricuspid stenoses in 24 (6%) and with tricuspid stenosis alone in 4 (1%). Therefore, if the 176 patients with associated aortic stenosis (24 of whom also had tricuspid stenosis) and the 65 with pure aortic regurgitation were excluded from the necropsy study (as they were in the present study), only 4 (2%) of the remaining 193 patients with mitral stenosis had associated tricuspid valve stenosis.[2]

Among patients with mitral stenosis severe enough to warrant a mitral valve operation, a significant percentage of them will also have some degree of pure tricuspid regurgitation. Of the 67 patients with replaced stenotic mitral valves in the present study, 58 (86%) had purely regurgitant tricuspid valves and 9 (14%) had stenotic tricuspid valves. The 58 purely regurgitant tricuspid valves were anatomically abnormal in 37 patients (64%) and anatomically normal in 21 (36%). We found only 1 previously published report with which our observations could be meaningfully compared. Hauck et al[4] examined operatively excised tricuspid valves in 248 patients with mitral stenosis, and 163 (66%) of them had purely regurgitant tricuspid valves and 85 (34%) had stenotic tricuspid valves. Of the 163 patients with purely regurgitant tricuspid valves, the tricuspid leaflets and chordae tendineae were anatomically normal in 54 (22%) and diffusely fibrotic in 194 (78%). The patients reported by Hauck and associates and by us underwent valve replacement during similar time periods (1963 to 1989). Comparison of these 2 studies indicates that the patients with mitral stenosis undergoing replacement of both mitral and tricuspid valves at the Mayo Clinic (Hauck et al) had a higher frequency of associated tricuspid valve stenosis and, therefore, a lower frequency of pure tricuspid regurgitation than those having similar therapy at the National Institutes of Health (present study).

Tricuspid valve replacement is performed less frequently today than during the 1960s and 1970s when 50 patients (75%) described in the present study underwent valve replacement operations. Justifying tricuspid valve replacement in the presence of tricuspid valve stenosis is much easier than justifying tricuspid valve replacement in the presence of pure tricuspid valve regurgitation associated with mitral stenosis. When the tricuspid leaflets and chordae are anatomically normal, as they were in 21 (31%) of the 67 patients described herein, we believe that most surgeons today would rarely replace the tricuspid valve. When the tricuspid valve is purely regurgitant but the leaflets are diffusely fibrotic, the decision of replacement versus anuloplasty (with ring) is more difficult. Unfortunately, in the present study none of the clinical or hemodynamic variables analyzed (Table I) was useful in distinguishing before surgery patients with purely regurgitant anatomically normal tricuspid valves from those with purely regurgitant anatomically abnormal ones.

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# Prognostic Features of Children with Idiopathic Dilated Cardiomyopathy

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**The presenting features and long-term outcome of 39 children (median age 6.5 months, range 1 day to 16 years) with idiopathic dilated cardiomyopathy (IDC) were reviewed to help determine the appropriate management of these patients. Four outcome groups were identified: those who died, improved, had IDC resolved or received transplants. Presenting clinical features of age, sex, race, congestive heart failure, cardiomegaly, and degree of systolic ventricular dysfunction did not predict final outcome. Left ventricular hypertrophy on the electrocardiogram was seen significantly more often in children who improved than in those who died or in whom IDC resolved ($p = 0.002$). A rhythm disturbance was also see more often in those who died than in those who survived ($p = 0.025$). Of 36 patients treated medically, 12 (33%) died, 15 (42%) improved and 9 (25%) resolved. Eighteen of 26 (69%) patients presenting at age ≤2 years survived, whereas 6 of 10 patients >2 years survived. There were no differences based on age at presentation, in the time to death or time of follow-up. Three patients received orthotopic heart transplants, 1 of whom died from graft failure. Thus, no clinical feature including age at presentation consistently predicts ultimate outcome in children with IDC.**

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Identifying the cause and managing children with idiopathic dilated cardiomyopathy (IDC) still presents a substantial clinical problem. Although extensive reports of IDC in adults are published,[1-3] only recently have additional reports added necessary information about the presentation and outcome of children with IDC.[4-6] Areas that require further information are the clinical progression of IDC, the appropriate use of diagnostic procedures such as endomyocardial biopsy, and the appropriate selection and timing of treatment modalities and transplantation. This report describes the presenting features, diagnostic evaluation and clinical outcome of a relatively large group of children with IDC from an entire state referral population and not just from a tertiary center. This information, combined with other reports, is important to help understand the nature of IDC in children and to establish appropriate management.

## METHODS

**Patient selection:** Subjects for this study were collected from the records of a state children's medical center and its consortium hospitals. Records between July 1966 and June 1990 were searched retrospectively for all patients with IDC as a primary diagnosis. Diagnosis was made on the basis of cardiomegaly or evidence of poor left ventricular systolic function by cardiac catheterization, echocardiography or autopsy in all cases. Patients with IDC secondary to arrhythmia or anatomic anomaly were excluded from the study, as were patients with hypertrophic or restrictive cardiomyopathy.

Charts of patients with IDC were reviewed for data on age and condition at initial presentation and at latest follow-up. Systolic left ventricular function was measured by the degree of fractional shortening in the minor axis (normal 31 to 42%). Left ventricular size at end-diastole was measured in the minor axis on M-mode recordings. To compare values with those of normal children, a ratio of measured end-diastolic dimension to the upper normal value for age and size was used. This value was labeled the left ventricular dimension ratio. A ratio of ≤1 indicates a ventricular dimension within 2 standard deviations of the mean.

**Analysis of data:** Each patient was followed until death, resolution of IDC, loss to follow-up, or through

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**TABLE I** Clinical Features of Children with Dilated Cardiomyopathy

| | | At Presentation | | | | | | | | At Follow-Up | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case | Sex | Age (mo) | CHF | Arrhyth. | LVH | CMCXR* | SF (%) | LVD Ratio | Follow-Up (mos) | CMCXR* | SF (%) | LVD Ratio | Outcome |
| 1 | F | Birth | + | — | — | + | 15 | — | 50 | + | 6 | 1.84 | Died |
| 2 | M | 0.2 | + | — | 0 | + | — | — | 0.03 | — | — | — | Died |
| 3 | F | 0.4 | + | + | 0 | + | — | 1.14 | 2 | — | 4 | 1.23 | Died |
| 4 | M | 1 | + | 0 | 0 | + | 8 | 1.15 | 0.75 | + | 8 | 1.15 | Died |
| 5 | M | 5 | + | + | + | + | — | — | 144 | + | — | — | Died |
| 6 | M | 6 | + | 0 | + | + | 13 | 1.36 | 7 | — | 16 | 1.33 | Died |
| 7 | F | 14 | + | 0 | 0 | + | 14 | 1.61 | 3 | — | 10 | 1.61 | Died |
| 8 | F | 16 | + | 0 | 0 | + | — | — | 2 | — | — | — | Died |
| 9 | F | 48 | + | 0 | 0 | + | 24 | 1.39 | 18 | — | 8 | 1.42 | Died |
| 10 | M | 84 | + | 0 | 0 | + | — | — | 4 | — | — | — | Died |
| 11 | M | 144 | + | + | 0 | + | — | — | 2 | | — | — | Died |
| 12 | F | 146 | + | + | 0 | + | 15 | 1.30 | 0.73 | — | 15 | 1.30 | Died |
| 13 | F | 2 | + | 0 | + | + | 11 | 1.15 | 252 | + | 23 | 1.16 | Improved |
| 14 | F | 3 | + | 0 | + | + | 25 | 1.60 | 4 | + | 33 | 1.38 | Improved |
| 15 | M | 3 | + | 0 | + | + | 18 | 1.56 | 108 | + | 20 | 1.40 | Improved |
| 16 | F | 3 | + | 0 | + | + | 13 | 1.33 | 96 | + | 37 | 1.08 | Improved |
| 17 | F | 4 | + | + | + | + | 17 | 1.17 | 84 | + | 24 | 1.21 | Improved |
| 18 | M | 4 | + | + | + | + | 27 | 1.11 | 194 | 0 | 30 | 1.11 | Improved |
| 19 | F | 6 | + | 0 | + | + | — | — | 204 | 0 | 27 | 0.88 | Improved |
| 20 | F | 7 | + | 0 | 0 | + | 17 | 1.89 | 64 | 0 | 30 | 1.18 | Improved |
| 21 | F | 7 | + | + | + | + | 22 | 1.89 | 10 | — | 18 | 1.25 | Improved |
| 22 | F | 7 | + | 0 | 0 | + | 23 | 1.30 | 223 | 0 | 32 | 1.02 | Improved |
| 23 | F | 7 | + | 0 | + | + | 9 | 1.81 | 98 | 0 | 27 | 1.25 | Improved |
| 24 | M | 21 | + | 0 | + | + | 12 | 1.33 | 23 | 0 | 23 | 1.29 | Improved |
| 25 | M | 36 | + | 0 | + | + | — | — | 90 | + | — | — | Improved |
| 26 | M | 48 | + | 0 | + | + | 9 | 1.56 | 36 | 0 | 19 | 1.30 | Improved |
| 27 | M | 192 | + | 0 | 0 | + | 16 | 1.35 | 22 | 0 | 26 | — | Improved |
| 28 | M | 0.15 | + | 0 | 0 | + | 28 | 1.00 | 36 | 0 | 32 | 1.03 | Resolved |
| 29 | F | 2 | + | 0 | 0 | + | 14 | 1.57 | 69 | 0 | 38 | 1.08 | Resolved |
| 30 | F | 6 | + | 0 | 0 | + | 16 | 1.92 | 84 | 0 | 32 | 1.10 | Resolved |
| 31 | F | 6 | + | 0 | 0 | + | 20 | 1.19 | 24 | 0 | 35 | 0.84 | Resolved |
| 32 | M | 6 | + | 0 | 0 | + | 23 | 1.71 | 27 | 0 | 38 | 1.03 | Resolved |
| 33 | M | 6 | + | 0 | 0 | + | 11 | 1.08 | 28 | 0 | 31 | 1.03 | Resolved |
| 34 | M | 27 | + | 0 | 0 | + | 17 | 1.55 | 95 | 0 | 34 | 0.97 | Resolved |
| 35 | F | 84 | 0 | 0 | + | + | — | — | 24 | 0 | — | — | Resolved |
| 36 | F | 180 | + | 0 | 0 | + | 14 | 1.37 | 30 | 0 | 32 | 1.13 | Resolved |
| 37 | M | 144 | + | + | + | + | 10 | 1.59 | 24 | 0 | 38 | 0.76 | Transplant |
| 38 | M | 156 | + | 0 | 0 | + | 3 | 1.55 | 22 | 0 | 36 | 1.03 | Transplant |
| 39 | M | 156 | + | 0 | 0 | + | 20 | 1.46 | 1 | — | 17 | 1.57 | Transplant & died |

*Cardiomegaly defined as cardiothoracic ratio >0.55.

Arrhyth. = arrhythmia; CHF = congestive heart failure; CMCXR = cardiomegaly on chest roentgenography; LVD = left ventricular dimension (see text); LVH = left ventricular hypertrophy; SF = shortening fraction; + = positive; 0 = negative; — = not done.

the most recent clinic visit. Only 3 patients were lost to follow-up 2, 7 and 15 years after initial diagnosis.

Patients were grouped by outcome—deceased, improved, IDC resolved or heart transplantation. To be classified as "resolved," a patient had to be clinically asymptomatic, be taking no cardiac medications, have no cardiomegaly (cardiothoracic ratio <55%), have normal left ventricular function and have a normal electrocardiogram. A patient was classified as improved if he showed improvement clinically or by test values, but did not meet all criteria for resolved. Patients who received transplants were treated as a separate category in all analyses because a heart transplant significantly changed the course of the disease.

**Statistical methods:** Because a normal distribution of variables among patients with IDC was not present, all statistical tests were nonparametric. For variables with numerical values, overall variation among outcome groups was investigated using the Kruskal-Wallis 1-way analysis of variance. For variables showing significant variation over all groups, pair-wise comparisons compared each 2 outcome groups using the Mann-Whitney U test. Variables that only had presence or absence of a feature were analyzed with the Fisher exact probability test. Actuarial survivorship was calculated using BMDP Statistical Software (BMDP Statistical Software, Inc., Los Angeles, California).

## RESULTS

**Patient demographics:** Thirty-nine patients were identified with IDC (Table I): 19 male and 20 female children; 23 were black and 16 were white. Median age

**TABLE II** Outcome of Dilated Cardiomyopathy in Children*

| | Died (%) | Survived (%) | Improved (%) | Resolved (%) |
|---|---|---|---|---|
| All patients (n = 36) | 12 (33) | 24 (67) | 15 (43) | 9 (25) |
| Patients presenting ≤2 years (n = 26) | 8 (31) | 18 (69) | 12 (46) | 6 (23) |
| Patients presenting >2 years (n = 10) | 4 (40) | 6 (60) | 3 (30) | 3 (30) |

*Excludes transplants.

at presentation was 6.5 months (range 1 day to 16 years). At presentation 26 (67%) were ≤2 years old and 13 (33%) were >2 years old.

**Follow-up and outcome:** The demographic data previously listed include all 39 patients. Of the 36 patients treated medically, 12 (33%) died, 15 (42%) improved and 9 (25%) had IDC resolved. Mean time to death was 19 months (mean ± standard deviation 40 months, range 1 day to 12 years). Time to death was not significantly different for those who presented at ≤2 years and those >2 years of age. Mean follow-up time for patients who survived was 80 months (± 70 months, range 4 months to 21 years). Eighteen of 26 patients (69%) ≤2 years at presentation survived, whereas 6 of 10 (60%) patients >2 years at presentation survived (Table II). Actuarial survivorship values at 1 and 5 years are shown in Figure 1. There was no correlation between sex, race, or age at presentation and survival or resolution.

**Clinical presentation:** Thirty-eight (97%) patients had signs of congestive heart failure. Only 1 patient had syncope. Eighteen patients (51%) had a precordial murmur. Serum carnitine levels measured in 15 patients were all normal. There was no significant correlation between outcome and any of the aforementioned features.

**Electrocardiography:** On presentation, 37 of 38 patients (97%) had an abnormal electrocardiogram (hypertrophy, conduction disturbance, or ST segment and T-wave abnormality), with 16 (42%) showing left ventricular hypertrophy (Table I). When deceased patients were compared with survivors, left ventricular hypertrophy was seen significantly less often in those who died (2 of 12 vs 13 of 24, $p < 0.05$). Likewise, left ventricular hypertrophy was seen less often in patients in whom it resolved than in those who improved (1 of 9 vs 12 of 15, $p = 0.002$). Of the 15 improved patients, 9 (60%) had continued electrocardiographic abnormalities at follow-up with 6 (40%) showing continued left ventricular hypertrophy.

On presentation, 9 (23%) patients had an arrhythmia of which 67% were ventricular in origin. Fifty percent of patients who died had an arrhythmia at presentation, whereas only 13% of survivors had an arrhythmia ($p < 0.025$).

**Chest roentgenography:** Every patient had cardiomegaly on chest roentgenography at presentation with no difference in outcome based on the cardiothoracic ratio. On follow-up, 7 of the 24 surviving patients (29%) all of whom were in the improved group, continued to have cardiomegaly.

**Echocardiography:** There was no significant correlation between outcome and either shortening fraction or left ventricular dimension ratio on presentation (deceased versus survivors, 13 ± 6% vs 16 ± 6%, p = not significant; and 1.33 ± 0.16 vs 1.45 ± 0.28, p = not significant).

**Biopsy results:** The last 14 consecutive children in this study had right ventricular endomyocardial biopsy. Thirteen patients had myocyte hypertrophy, enlarged irregularly shaped nuclei and increased fibrosis on light microscopy evaluation, consistent with IDC. The other

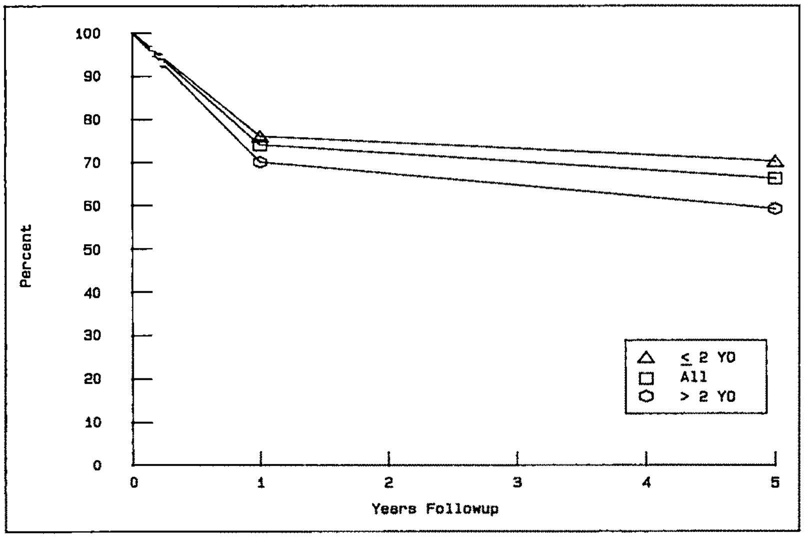

**FIGURE 1. This graph shows the actuarial survival of children with dilated cardiomyopathy at 1 and 5 years after diagnosis. Survival of children presenting at ≤2 years of age and >2 years of age has no statistically significant difference. YO = years old.**

**TABLE III** Outcome of Dilated Cardiomyopathy in Children Reported in Studies Based on Age at Presentation

| | | | | <2 Years | | | >2 Years | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of Pts. | Died (%) | Survived (%) | No. | Died (%) | Survived (%) | No. | Died (%) | Survived (%) |
| Greenwood et al[7] | 161 | 57 (35) | 104 (65) | 99 | 32 (32) | 67 (68) | 62 | 25 (40) | 37 (60) |
| Chen et al[6] | 23 | 11 (48) | 12 (52) | 10 | 5 (50) | 5 (50) | 13 | 6 (46) | 7 (54) |
| Taliercio et al[4] | 24 | 15 (63) | 9 (38) | 12 | 4 (33) | 8 (69) | 12 | 11 (92) | 1 (8) |
| Griffin et al[5] | 32 | 17 (53) | 15 (47) | 20 | 5 (25) | 15 (75) | 12 | 12 (100) | |

remaining patient had areas of focal lymphocytic infiltration with myocyte necrosis, representing acute myocarditis. One other patient had an increased number of lymphocytes throughout the myocardium but no areas of myocyte necrosis.

**Treatment:** Thirty-six patients received only medical treatment. Thirty-four (94%) were treated with inotropic agents, 21 (58%) with afterload reducers, 6 (17%) with antiarrhythmic drugs, and 2 (6%) with antiinflammatory agents. There was no significant correlation between outcome and type of medical management.

**Transplantation:** Three patients received cardiac transplants (Table I). There were no significant differences in clinical presentation between the transplant recipients and other patients. One transplant recipient died after 2 cardiac grafts failed, 1 month after diagnosis.

## DISCUSSION

**Outcome:** Four follow-up groups of children presenting with IDC were found: those who died, those who improved after presentation but did not have return of normal ventricular function, those in whom IDC resolved, and those who underwent transplantation. The definition for "resolved" was strict and included normal left ventricular systolic function, normal heart size, normal electrocardiogram, no clinical symptoms and requiring no cardiac medication. The group with transplantation must be considered separately in follow-up because this surgical procedure drastically alters the course of IDC. The outcome of the 36 children who received medical therapy included 33% who died, 42% who improved and 25% in whom IDC resolved. These numbers correspond closely to the results of Greenwood et al[7] who reviewed the course of 161 pediatric patients with "primary myocardial disease" (Table III). Other studies[4-6] have shown higher mortality rates of 48 to 63% (Table III).

The small number of patients undergoing transplantation in this study does not allow comparison of outcome with those receiving medical therapy alone; however, the 1990 International Society of Heart Transplantation Registry records a worldwide 1-year survival in pediatric patients of approximately 70%. This does not differ from the 67% survival of transplanted patients in this study or the 67% survival of medically treated patients. Until diagnostic evaluation can accurately differentiate between the one-third who die, the one-third who improve and the one-third in whom IDC resolves, timing of transplantation for children with IDC remains a difficult problem.

**Age:** Griffin et al[5] reported a difference in outcome depending on age at presentation. All patients who presented at >2 years of age died, whereas only 25% of patients presented at ≤2 years old died. Taliercio et al[4] did not discuss patients by age at presentation, but presented sufficient data to show that 33% of children presenting ≤2 years of age died, whereas 92% of children presenting at >2 years old died. The reports of Greenwood et al[7] and Chen et al,[6] however, showed no significant differences in outcome based on age at presentation (Table III). The study population in this report showed a slightly higher mortality in patients presenting at >2 years (40 vs 31%), but this did not reach statistical significance. This finding may reflect the fact that this report covered an entire state population and not only patients referred to a tertiary center.

**Chest roentgenography and echocardiography:** Most investigators of IDC in children and adults have found no significant differences in presenting clinical signs.[4-9] Heart size at presentation as measured by cardiothoracic ratio on chest roentgenography did not predict outcome in this study. As with chest roentgenography, measurement of left ventricular indexes, shortening fraction and end-diastolic dimension on presentation provided no prognostic information. Follow-up echocardiography near the time of death or long term again showed that patients who died had worse left ventricular function as measured by these parameters. Further prospective study may indicate that how rapid or slow function returns may predict eventual outcome.

**Electrocardiography:** Studies of adults and children have shown that atrial and ventricular arrhythmias are poor prognostic signs in patients with IDC.[5,8] Only 15%

of the patients in this study presented with ventricular ectopy, and their long-term outcome was worse. The absence of left ventricular hypertrophy on the presenting electrocardiogram showed a statistically significant difference between death or resolution and improvement. Other reports have noted a similar finding in adults[10,11] but not in children.[4] The theory explaining this finding is that myocardial hypertrophy reduces wall stress. This theory applies to the difference seen between patients who died and those who improved, but it does not separate the patients who died and those who ultimately had a complete resolve of IDC. The patients who had resolution of IDC must have had significantly less disease, but no other clinical test at presentation in this series allowed prediction of outcome.

**Myocarditis:** The association of myocarditis and IDC has always been assumed. The clinical cliché that IDC represents "burned out myocarditis" is hardly ever convincingly proved. The number of cases of biopsy-prove myocarditis in children presenting with unexplained IDC appears small. Lewis et al[12] found no evidence of myocarditis in 15 children. Leatherbury et al[13] obtained biopsy specimens from 20 children and found myocarditis in 25%, but 1 of these had sarcoidosis and another had transplacental antinuclear antibodies from maternal systemic lupus erythematosus. These do not represent the typical case of a child presenting with IDC and possible myocarditis. Only 1 of 14 (7%) patients undergoing a biopsy procedure in this study had evidence of myocarditis by the criteria of Aretz et al.[14] Overall, the incidence of biopsy-proved myocarditis in children presenting with IDC appears to be 2 to 15%.

**Study limitations:** This report, as with all others, is a retrospective review of patients over a relatively long period of time and has its shortcomings. Diagnostic techniques varied over this time period, so careful attention was paid to help eliminate conditions not representing IDC. Because we cannot differentiate the many causes of dilated cardiomyopathy, information on outcome cannot be specifically grouped based on cause. Using chart review, we were unable to gather enough information to track the rate of recovery in patients who survived. The rate of recovery may be the best indicator of ultimate outcome.

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# Effect of Digoxin on Contractility and Symptoms in Infants with a Large Ventricular Septal Defect

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**The effect of digoxin on contractility and symptoms in infants with a large ventricular septal defect (VSD) is controversial. Nineteen infants with symptoms of congestive heart failure due to a VSD were studied with load-independent indexes during 4 study periods: (1) before any medication; (2) while on chronic diuretics; (3) while on both diuretics and digoxin; and (4) while on diuretics alone, to determine if digoxin: (a) increases "contractility" when added to diuretic therapy; and (b) improves symptoms. Symptoms, signs (heart and respiratory rates, and weight gain), shortening fraction, preload (left ventricular end-diastolic dimension), afterload (left ventricular end-systolic wall stress) and contractility were measured at each period. The difference between the measured and predicted velocities of circumferential fiber shortening for the measured left ventricular end-systolic wall stress served as an index of contractility. Eighteen infants also underwent catheterization. Mean pulmonary-to-systemic blood flow ratio was 3:1. When digoxin was added to diuretics, contractility index was significantly greater than in control subjects (0.13 ± 0.15 vs 0.0 ± 0.12 circ/s, $p = 0.04$). When patients were again on diuretics alone (after discontinuation of digoxin), contractility index was no longer different. Symptoms and signs were not significantly improved by either diuretics or digoxin.**

**It is concluded that in infants with a large left-to-right VSD shunt and receiving digoxin and diuretics, contractility index was significantly greater than in control subjects. However, neither diuretics alone nor in combination with digoxin improved symptoms significantly.**

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Whereas some pediatric cardiologists routinely give digoxin and diuretics to infants with symptoms of tachypnea, tachycardia and growth failure due to a large shunt through a ventricular septal defect (VSD), others question the usefulness of digoxin in these patients. Symptoms may not be due to myocardial failure, but rather to pulmonary overcirculation.[1–5] Furthermore, the benefit of digoxin on contractility or symptoms has not been clearly demonstrated.[4,6] This is partly due to the reliance on ejection phase indexes that change not only with contractility but also with loading conditions. Recent advances now allow echographic measurement of contractility while taking into account loading conditions.[7] The purposes of this study were to determine in infants with symptoms of congestive heart failure due to a large VSD shunt if: (1) cardiac contractility improves when digoxin is added to diuretic therapy alone; and (2) symptoms of heart failure improve with digoxin and diuretic treatment.

## METHODS

**Patients:** Infants with symptoms of tachypnea, tachycardia, growth failure and excessive diaphoresis due to large left-to-right VSD shunting were eligible for inclusion in this study. Nineteen patients participated in the protocol after informed consent was obtained. The control group consisted of 17 infants without heart disease.

**Study protocol:** The study protocol consisted of 4 periods of clinical and echocardiographic evaluations. The first examination was performed at baseline before any medications had been administered. The second examination occurred after beginning oral diuretics (furosemide 2 to 3 mg/kg/day and spironolactone 1 to 2 mg/kg/day). The third evaluation occurred after oral digoxin (10 μg/kg/day) had been added to the diuretics and only after a therapeutic serum digoxin level had been obtained. The fourth and final examination occurred after digoxin had been stopped while diuretics were continued.

During each study period patients underwent physical examinations, electrocardiography and echocardiography, and history was obtained. Serum electrolytes were obtained during the second and third study periods. During the third study period, serum digoxin levels

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were measured with an immunoassay technique (Abbott Diagnostics). Oxygen, blood transfusion, vasodilators or salt restriction, or a combination, were not part of the treatment regimen.

**Clinical assessment:** During each study patients were assigned to 1 of 4 clinical classes using a heart failure classification system adapted especially for infants and previously described by our laboratory[8]: no symptoms (class I); tachypnea or diaphoresis with feedings, and no growth delay (class II); tachypnea or diaphoresis with feeding, without weight gain (class III); and symptomatic at rest with tachypnea, retractions, grunting and diaphoresis, without weight gain (class IV). In addition, respiratory and heart rates, and weight were recorded at each evaluation.

**Echocardiographic assessment:** Each patient underwent 2-dimensional and pulsed Doppler examinations using the Hewlett-Packard model 77020AC Ultrasound Imaging System. M-mode echocardiography was performed with either the Hewlett-Packard or an Irex System II Ultrasound System. Echocardiography was performed in a quiet, resting state; chloral hydrate (50 to 80 mg/kg) or pentobarbital (3 to 4 mg/kg), or both, were used for sedation when necessary. Simultaneous phonocardiogram, electrocardiogram and indirect axillary pulse tracing were also recorded. Peak systolic and diastolic blood pressures were obtained from a Dinamap 845-XT Vital Signs Monitor (Critikon). Left ventricular end-diastolic and end-systolic dimensions, and left ventricular end-systolic wall thickness were measured. Shortening fraction, heart rate-corrected velocity of circumferential fiber shortening ($Vcf_c$), and left ventricular end-systolic meridional wall stress were calculated.[7,9,10]

Contractility was assessed by examining the relationship between $Vcf_c$ and end-systolic wall stress, as previously described.[5,11-14] In a previous study Colan et al[7] showed that the slope of this relation remained constant over a wide range of wall stress during positive inotropic intervention. Therefore, as previously published,[5,11] the difference between measured and predicted $Vcf_c$ for measured end-systolic wall stress (as established in the control group) served as an index of contractility in the patients at each study period.

VSD size was measured at the initial and final studies by off-line analysis of 2-dimensional images, using a Digisonics Echocardiography Analysis System and indexed by dividing by body surface area, as previously described.[5] To determine the degree of circularity of the transverse plane of the left ventricle, diameters were measured along 2 axes in the parasternal short-axis view: (1) from the midseptum to posterior wall of the left ventricle; and (2) from the anterior to the inferior wall of the left ventricle. Circularity was estimated from the ratio of these 2 perpendicular diameters.

All echocardiographic measurements were obtained by 1 of the investigators (TRK) or a technical assistant, both of whom were unaware of patient identity and medication use. Intra- and interobserver variabilities of $Vcf_c$ and wall stress were determined from the echocardiograms of the control patients.

**Catheterization assessment:** Eighteen of the 19 patients with VSD underwent cardiac catheterization at 5.7 ± 3.0 months old. Intravenous ketamine was used for sedation. Oxygen consumption and saturations were recorded. Pressures were obtained from a fluid-filled catheter system. Cardiac outputs were measured by the Fick method. Because ketamine may increase pulmonary vascular resistance, pulmonary-to-systemic blood flow ratios may be underestimated in this study.

**Statistical analysis:** Simple linear regression (least-squares method) was used to fit each control subject's data to a wall stress—$Vcf_c$ equation ($Vcf_c$ = m (wall stress) + b; m = slope, b = y intercept). Analysis of variance for repeated measures was utilized to compare means of the groups using the General Linear Model procedure. This was followed by multiple comparisons using Duncan's procedure when needed. The data were also analyzed by paired *t* tests. This was necessary since there were varying numbers of data points for various groups and time points. Analysis of variance for repeated measures used only subjects with data in all time points, thus reducing the total sample size. Results were similar for both statistical methods (i.e., paired *t* tests or repeated measures analysis of variance). All the calculations were performed using the computer software package Statistical Analysis System version, 5th edition (SAS Institute, Cary, North Carolina). Statistical significance was claimed at a p value $<0.05$.

## RESULTS

Twelve of the 19 patients entered at the first study period, whereas the remaining 7 who were already receiving diuretics entered at the second study period. One patient did not undergo a second study because his attending cardiologist believed that his condition necessitated concomitant administration of both diuretics and digoxin. In 2 other patients surgery was thought to be indicated after the third study. Thus, 11 comparisons of baseline versus diuretic treatment, 18 of diuretics alone versus both digoxin and diuretics, and 17 of both digoxin and diuretics versus diuretics alone after digoxin withdrawal were available for analysis.

The second examination occurred after 2.8 ± 2.3 weeks of diuretic therapy, and the third occurred 2.8 ± 2 weeks after digoxin was added to diuretics. Serum

**TABLE I** Catheterization Data

| Pt. No. | Qp/Qs | PAP (mm Hg) | PVR (Wood units x m$^2$) | SVR (Wood units x m$^2$) | PVR/SVR | RVP/LVP | VO2 (ml/min x m$^2$) |
|---|---|---|---|---|---|---|---|
| 1 | 5.5 | 48 | 2.5 | 21 | 0.12 | 0.75 | 114 |
| 2 | 1.9 | 35 | 1.2 | 13 | 0.09 | 0.47 | 150 |
| 3 | 2.2 | 27 | 0.8 | 11 | 0.07 | 0.65 | 189 |
| 4 | 3.1 | 26 | 1.2 | 17 | 0.07 | 0.49 | 188 |
| 5 | 2.0 | 18 | 1.3 | 12 | 0.11 | 0.36 | 156 |
| 6 | 2.0 | 27 | 3.1 | 22 | 0.14 | 0.72 | 130 |
| 7 | 2.4 | 53 | 5.5 | 22 | 0.25 | 0.97 | 115 |
| 8 | 4.2 | 18 | 0.6 | 15 | 0.04 | 0.71 | 170 |
| 9 | 2.5 | 32 | 2.6 | 20 | 0.13 | 0.88 | 141 |
| 10 | 6.7 | 25 | 1.4 | 23 | 0.06 | 0.75 | 138 |
| 11 | 1.8 | 26 | 3.5 | 17 | 0.21 | 0.50 | 99 |
| 12 | 4.2 | 38 | 2.1 | 26 | 0.08 | 0.77 | 150 |
| 13 | 2.3 | 25 | 1.3 | 9 | 0.14 | 0.53 | 211 |
| 14 | 5.2 | 31 | 1.6 | 20 | 0.08 | 0.77 | 180 |
| 15 | 2.1 | 16 | 1.8 | 23 | 0.08 | 0.47 | 202 |
| 16 | 2.8 | 35 | 1.7 | 17 | 0.10 | 0.78 | 88 |
| 17 | 3.2 | 58 | 6.0 | 23 | 0.26 | 0.94 | 160 |
| 18 | 2.1 | 43 | 4.5 | 17 | 0.26 | 0.69 | 143 |
| Mean ± SD | 3.1 ± 1.4 | 32 ± 12 | 2.4 ± 1.6 | 18 ± 5 | 0.13 ± 0.07 | 0.68 ± 0.17 | 151 ± 35 |

LVP = peak systolic left ventricular pressure; PAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; $Q_p$ = pulmonary blood flow; $Q_s$ = systemic blood flow; RVP = peak systolic right ventricular pressure; SD = standard deviation; SVR = systemic vascular resistance; VO2 = oxygen consumption.

digoxin levels averaged 1.3 ± 0.4 ng/ml at that time. The fourth evaluation occurred 4.2 ± 3.1 weeks after digoxin had been stopped.

**Demographic data:** The median age and weight of the patients were 2.5 months (standard deviation [SD] = 3.1) and 4.9 kg (SD = 1.9), respectively. These were not significantly different from the control group's age (median = 5 months, SD = 3.6) and weight (median = 7.9 kg, SD = 2.3). In the control group, the relation between $Vcf_c$ and end-systolic wall stress was inversely linear and was described by the equation $Vcf_c = -0.0089$ (wall stress) + 1.49 (Figure 1).

**Ventricular septal defect characteristics:** Mean and indexed VSD sizes at study entry were 0.95 ± 0.22 cm and 3.7 ± 0.8 cm/m$^2$, respectively, and did not change significantly by the end of the study protocol (0.98 ± 0.20 cm and 3.2 ± 0.7 cm/m$^2$, respectively; p = not significant).

Catheterization data are listed in Table I. Mean pulmonary-to-systemic blood flow ratio was 3.1, and mean pulmonary-to-systemic vascular resistance ratio was 0.13. Seventeen of the patients subsequently underwent surgical closure of their VSD shortly after completion of the protocol.

**Variability of heart rate-corrected velocity of circumferential shortening, and end-systolic wall stress:** The interobserver variability of $Vcf_c$ and end-systolic wall stress was 3.6 and 5.5%, respectively. The intraobserver variability of $Vcf_c$ and end-systolic wall stress was 2.3 and 3.5%, respectively. Linear regression demonstrated excellent correlation for separate observers determining $Vcf_c$ (r = 0.91) and end-systolic wall stress

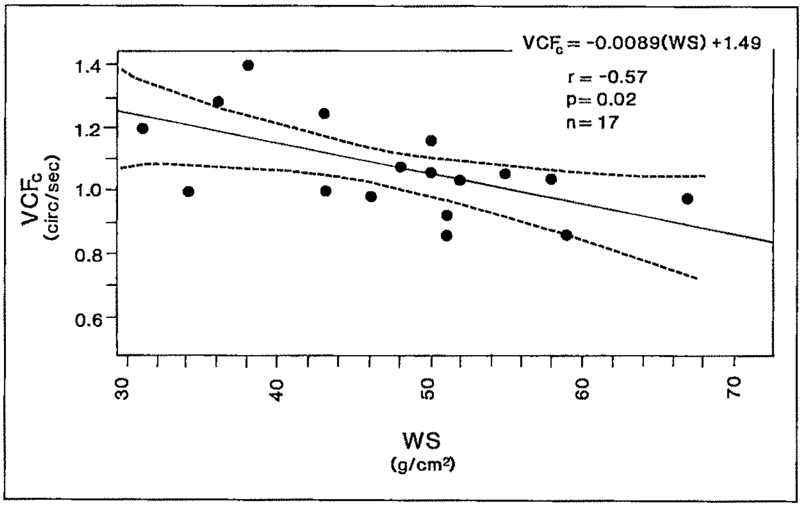

**FIGURE 1. Heart rate-corrected velocity of circumferential fiber shortening ($VCF_c$) and left ventricular end-systolic wall stress (WS) data points for control subjects. Fitted line *(solid line)* and 95% confidence limits *(dashed lines)* are also shown.**

**TABLE II** Echocardiographic and Clinical Data at Each Study Period

| | Medication Status | | | | | |
|---|---|---|---|---|---|---|
| | None (n = 11) | Diur. (n = 11) | Diur. (n = 18) | Dig. & Diur. (n = 18) | Dig. & Diur. (n = 17) | Diur. (n = 17) |
| SF (%) | 31 ± 8 | 35 ± 5* | 32 ± 7 | 33 ± 4 | 34 ± 4 | 34 ± 9 |
| LVED (cm) | 2.6 ± 0.5 | 2.6 ± 0.5 | 2.6 ± 0.5 | 2.6 ± 0.5 | 2.7 ± 0.5 | 2.7 ± 0.5 |
| $Vcf_c$ (circ/s) | 1.06 ± 0.28 | 1.18 ± 0.14 | 1.08 ± 0.22 | 1.16 ± 0.17 | 1.16 ± 0.18 | 1.07 ± 0.27 |
| WS (g/cm$^2$) | 64 ± 42 | 56 ± 23 | 55 ± 20 | 51 ± 15 | 52 ± 16 | 49 ± 17 |
| HR (beats/min) | 140 ± 19 | 142 ± 17 | 141 ± 18 | 139 ± 16 | 137 ± 12 | 136 ± 13 |
| RR (breaths/min) | 61 ± 20 | 62 ± 11 | 64 ± 15 | 64 ± 19 | 62 ± 19 | 57 ± 15 |
| Wt (percentile) | 32 ± 31 | 22 ± 21* | 25 ± 26 | 24 ± 27 | 23 ± 26 | 19 ± 23 |

*$p < 0.05$.

Data are expressed as mean ± standard deviation.

Dig. = digoxin; Diur. = diuretics; HR = heart rate; LVED = left ventricular end-diastolic dimension; None = no medications; RR = respiratory rate; SF = shortening fraction; $Vcf_c$ = heart rate-corrected velocity of circumferential shortening; WS = left ventricular end-systolic wall stress; Wt = percentile for weight.

(r = 0.93). Correlations were also excellent for 1 observer repeating determinations of $Vcf_c$ (r = 0.96) and end-systolic wall stress (r = 0.95).

**Echocardiographic data:** The average ratios of septoposterior to anteroinferior free wall diameter in patients with VSD were 0.94 ± 0.13 in diastole and 0.99 ± 0.11 in systole. These ratios were not statistically different from a ratio of 1. Thus, the transverse geometry of the left ventricle was circular.

Echocardiographic data for the patients at each study period are listed in Table II. Shortening fraction significantly increased from baseline levels with the addition of diuretics alone. However, there were no significant differences in left ventricular end-diastolic dimension and wall stress among the study periods.

There was a slight increase in contractility index (Figure 2) between control subjects and patients with VSD receiving no medications. There was a further slight increase in contractility index in patients when digoxin was added to diuretics. Neither of these differences was statistically significant by itself; however, the cumulative effect resulted in a significantly higher contractile index in patients receiving both digoxin and diuretics compared with that in control subjects. Subsequent withdrawal of digoxin was associated with a decrease in contractility index, but again this change was not statistically significant.

**Clinical data:** No patient was asymptomatic (class I) at the beginning of the study. Although 1 patient did improve to class I clinical status while receiving digoxin and diuretics together, medical treatment (either diuretics alone or digoxin with diuretics) did not significantly improve clinical status of the group. There were no significant changes in heart and respiratory rates during the protocol. When patients were receiving diuretics alone they had significantly lower weight percentiles compared with when they were receiving no medications. In addition, there was a further significant

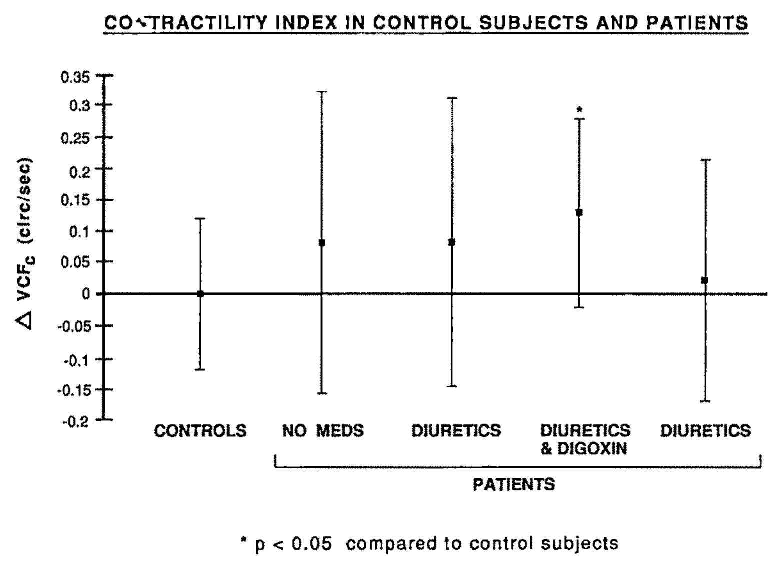

**FIGURE 2. Contractility index in control subjects and patients. Data are expressed as mean ± standard deviation. Δ $VCF_c$ = difference between predicted and measured heart rate-corrected velocity of circumferential fiber shortening for measured left ventricular end-systolic wall stress.**

decrease in weight percentile during the remainder of the study protocol (25th ± 26th to 19th ± 23rd percentile; $p = 0.03$).

## DISCUSSION

Whereas digoxin has been shown to be of benefit to adults with heart failure,[15] some investigators question its effectiveness.[16] These studies of the effect of digoxin in adults have been performed in patients with impaired contractility. The infant who has symptoms due to a large left-to-right shunt may have normal contractility.[1-5,17] Therefore, the use of digoxin in infants with large left-to-right shunts is controversial.[4,6,18-22] Several investigators have found that digoxin increases ventricular performance,[19-21] whereas others have found little or no change in function.[6,22] Furthermore, it appears that clinical improvement may not always be associated with improvement in ventricular function.[6]

Previous studies are limited because of the use of ejection phase indexes that are dependent on loading conditions and may be unreliable in the presence of VSD.[23] Although the model for deriving contractility in our study has geometrical constraints (i.e., it assumes that the left ventricle is ellipsoidal, has uniform and thin-walled thickness, and is symmetric along its minor axis), our data indicate that the transverse axis of the left ventricle of our patients with VSD maintained a circular configuration. Therefore, the major assumption of the model is satisfied and should be accurate.

As previously suggested,[5] we found that patients with large VSD shunts before receiving medication have higher contractility indexes than control subjects have (although not significantly so). Perhaps elevated circulating catecholamines in these symptomatic patients may raise contractility. Further investigation is needed to examine potential mechanisms.

The addition of digoxin to diuretics in our patients further increased contractility to a level significantly higher than control subjects. However, the incremental increase in contractility with the addition of digoxin was not significant compared with that while receiving diuretics alone. Likewise, the incremental decrease in contractility associated with digoxin withdrawal was not statistically significant.

Despite the observations of many clinicians that symptoms improve when digoxin and diuretics are used in these patients, our study does not support this finding. It is possible that the effects of these 2 medications could have been acutely different after their initiation. These more acute data were not specifically measured in this study. It is also possible that our assessment scale may not have been sensitive enough to detect subtle clinical changes, but the objective parameters of weight gain, and respiratory and heart rates also did not improve. In fact, weight percentile significantly decreased when patients were placed on diuretics and continued to do so throughout the study protocol. Although the initial decrease in weight percentile associated with diuretics was most likely due to excess water loss, the continued decrease in the patients' weight percentiles during the remainder of the protocol was most likely due to increased caloric expenditure due to the large VSD. Therefore, even though the combination of digoxin and diuretics in VSD patients increased contractility over control subjects, this effect was not apparent clinically.

The patients in this study represent a subset of patients who had a particularly large left-to-right VSD shunt and were very ill compared with other patients with VSD.[5] Indeed, 17 of these 19 patients eventually underwent surgery to control their symptoms. The effects of digoxin and diuretics in patients with smaller VSD who are less seriously ill may be different and cannot be determined from this study.

The statistical nonsignificance of pairwise differences in contractility does not necessarily mean that contractility was equivalent at different medication states. Although inter- and intraobserver variabilities were less, there was quite a bit of variability in these measurements between patients. The sample size may have been small enough that statistical significance could not have been achieved. However, we did find a statistically significant difference in contractility between control subjects and patients receiving digoxin and diuretics that did not result in clinical improvement.

The value of digoxin in infants with symptoms due to a large VSD shunt is questionable. In addition, the use of digoxin may be undesirable because it can potentiate the complication of rhythm disturbance in conjunction with diuretic therapy. Because of the questionable value and potential risk of digoxin, alternative treatments, such as afterload reducing agents or earlier surgical intervention, may need to be considered.

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# Age-Related Variation in Contractility Estimate in Patients ≤20 Years of Age

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**The relation between velocity of circumferential fiber shortening (VCF) and wall stress (WS) is being used to estimate contractile state in a variety of disease states and patient ages more frequently. However, its relation to age has not been established. To determine reproducibility and age and sex dependence of this relation, 204 normal children (113 boys, 91 girls) underwent echographic determination of VCF and WS. The children were enrolled in 3 groups: group 1 <6 months old (n = 27); group 2 >6 months and <3 years old (n = 38); and group 3 >3 and <20 years old (n = 139). Twenty-five children also underwent serial echocardiography (n = 44) to determine reproducibility of the relation. Only 1 of the 44 repeat data pairs of VCF and WS was outside the 95% confidence limits of that relation. In all 3 groups, VCF was significantly inversely and linearly related to WS (p <0.001). The regression equation in the oldest group was very similar to previous reports (VCF = −0.0031 [WS] + 1.21). The regression lines in the 2 younger groups were significantly steeper and had a significantly higher y-intercept (p <0.01). Group 1 had the steepest slope and highest y-intercept. There was no difference in the regression lines of different sexes in any of the patient groups. It is concluded that the relation of VCF to WS is reproducible over time. It is age-dependent but has no relation to gender. VCF in patients <6 months old is more highly dependent on WS. Clinician and investigators need to select the appropriate age-related relation to study contractility in young patients.**

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The relation between heart rate–corrected velocity of circumferential fiber shortening (VCF) and end-systolic wall stress (WS) is being used to noninvasively examine contractile state in patients with a variety of disease states and ages.[1-4] The normal relation with confidence bands serves to define normal contractility. The vertical distance between a data point and the normal regression line serves as a quantitative estimate of contractility.[1] Although the normal relation has been established with reasonable certainty in children >3 years,[5] it has not been extensively studied in younger children. Because animal research indicates that young lambs have a different inotropic state than adult lambs,[6-9] this would suggest the possibility of a different VCF to WS relation in younger patients. To examine contractility and to apply the relation between VCF and WS to the clinical setting in young patients, the relation must first be established in normal subjects of young age. This study determines (1) the reproducibility of VCF to WS determinations, (2) if there are age-related changes in contractility as estimated by the relation between VCF and WS, and (3) if there is an association of gender to this relation.

## METHODS

**Patients:** Two hundred four patients (113 boys, 91 girls) were studied. No patient had symptoms of cardiac disease. All patients had normal physical examinations and echocardiograms. The patients were divided into 3 groups based on age. Group 1 (n = 27) was <6 months old; group 2 (n = 38) was >6 months and <3 years old; group 3 (n = 139) was >3 and <20 years old. These age groupings were chosen in order to explore differences by age suggested in previous investigations and to compare data with these studies.[5] The characteristics of each group are summarized in Table I. There were no significant differences in the sex distribution between the 3 groups.

**Echocardiography:** All patients underwent 2-dimensional, pulsed Doppler and color flow examination using a Hewlett-Packard model 77020AC Ultrasound Imaging System. M-mode echocardiography was performed with either this system or an IREX System II Ultrasound Machine. Chloral hydrate (50 to 80 mg/kg) was used for sedation when necessary. Phonocardiograms, electrocardiograms, and indirect carotid or

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**TABLE I** Patient Characteristics

| | Group 1 <6 m.o. (n = 27) | Group 2 >6 m.o., <3 y.o. (n = 38) | Group 3 >3 y.o., <20 y.o. (n = 139) |
|---|---|---|---|
| Age | 77 ± 51 days | 17 ± 9 months | 9 ± 4 years |
| Weight (kg) | 5.6 ± 1.8 | 11.5 ± 5.3 | 32.6 ± 16.9 |
| Male/female | 16/11 | 24/14 | 73/66 |

Data are expressed as mean ± standard deviation.
m.o. = months old; y.o. = years old.

axillary pulse tracings were simultaneously recorded. Peak systolic and diastolic blood pressures were obtained from a Dinamap 845-XT Vital Signs Monitor (Critikon). M-mode data consisted of left ventricular end-diastolic and end-systolic dimensions (LVED, LVES) and wall thicknesses ($h_{ed}$, $h_{es}$) and end-diastolic septal thickness(s). End-systole was defined as the first component of the second heart sound.

Left ventricular ejection time ($ET_c$) was derived from the pulse trace and rate-corrected to a heart rate of 60 beats/min by dividing by the square root of the RR interval.[10] The pulse trace was calibrated by assigning the systolic blood pressure to the peak and the diastolic blood pressure to the nadir of the trace. The end-systolic pressure (P) was obtained by linear interpolation to the dicrotic notch.[5]

Shortening fraction (SF = [LVED − LVES]/LVED) and heart rate–corrected VCF (VCF = SF/$ET_c$) were calculated. Left ventricular end-systolic meridional WS was determined by the method of Grossman et al,[11] which has been validated by Lang et al[12]:

$$WS(g/cm^2) = \frac{(1.35)(P)(LVES)}{(4)(h_{es})(1 + h_{es}/LVES)}$$

where 1.35 is the conversion factor from mm Hg to g/cm². This is a reliable index of afterload.[12]

Left ventricular mass was calculated from the methods of Devereux et al[13]:

$$LV\ mass(g) =$$

$$[(0.8)(1.04)(LVED + h_{ed} + s)^3 - (LVED^3)] + 0.6$$

This was indexed by dividing by body surface area.

Six cardiac cycles were measured for each patient. All echocardiographic measurements were made by sonographers with special expertise in WS determination and who were unaware of patient status and age. With use of these techniques, intra- and interobserver variability is excellent within our laboratory.[14]

**Reproducibility of velocity of circumferential fiber shortening to wall stress determinations:** Twenty-five patients underwent a total of 44 repeat echocardiograms (2 to 5 repeat studies per patient) at 1-day to 43-month intervals to determine the reproducibility of the VCF to WS relation. No patient received any cardioactive or cardiotoxic medication during this period.

**TABLE II** Echocardiographic Results

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Left ventricular end-diastolic dimension (cm) | 2.1 ± 0.3 | 2.8 ± 0.3* | 3.8 ± 0.5*† |
| Left ventricular end-systolic dimension (cm) | 1.4 ± 0.2 | 1.8 ± 0.3* | 2.5 ± 0.4*† |
| Left ventricular end-diastolic wall thickness (cm) | 0.3 ± 0.09 | 0.4 ± 0.09 | 0.5 ± 0.16*† |
| Left ventricular end-systolic wall thickness (cm) | 0.7 ± 0.13 | 0.7 ± 0.15 | 1.1 ± 0.2*† |
| End-diastolic septal thickness (cm) | 0.3 ± 0.08 | 0.4 ± 0.07 | 0.5 ± 0.14*† |
| Left ventricular end-systolic pressure (mm Hg) | 73 ± 12 | 77 ± 12 | 82 ± 10*† |
| Shortening fraction (%) | 35 ± 6 | 36 ± 5 | 34 ± 6 |
| Heart rate–corrected velocity of circumferential fiber shortening (circ/s) | 1.15 ± 0.2 | 1.09 ± 0.12 | 1.06 ± 0.17* |
| Wall stress (g/cm²) | 36 ± 11 | 46 ± 15* | 48 ± 13* |
| Mass (g/m²) | 34 ± 12 | 38 ± 10 | 48 ± 13*† |

*p <0.05 compared with group 1; †p <0.05 compared with group 2.
Data are expressed as mean ± standard deviation.
Group 1 = patients <6 months old; group 2 = patients >6 months and <3 years old; group 3 = patients >3 and <20 years old.

**Statistical analysis:** To investigate reproducibility, each VCF, WS pair for the 44 repeat studies was compared with the confidence limits established for the age-appropriate study population to determine if there was consistency of the determinations of contractile state.

Unadjusted means for echographic variables were compared between each group and differences were tested for significance by pairwise *t* tests. Analysis of covariance was performed to find a model to fit the relationship of VCF and WS. Independent variables considered in the analysis included weight, age, (age)² and sex. The same analysis was performed with the subjects divided into the 3 age groups. Using the general linear models program (GLM) in SAS (SAS Institute, Carey, North Carolina), a model of VCF and WS was obtained. This model tested for differences between individual regression lines for each group, as well as the main effect of WS on VCF. Mean values of VCF were compared between the groups after adjusting for the effect of WS.

## RESULTS

**Echocardiographic data:** The echocardiographic results are summarized in Table II. As expected, left ventricular end-diastolic and end-systolic dimensions and thicknesses increased significantly between groups. Although there were no significant differences in shortening fraction, VCF was significantly higher in group 1

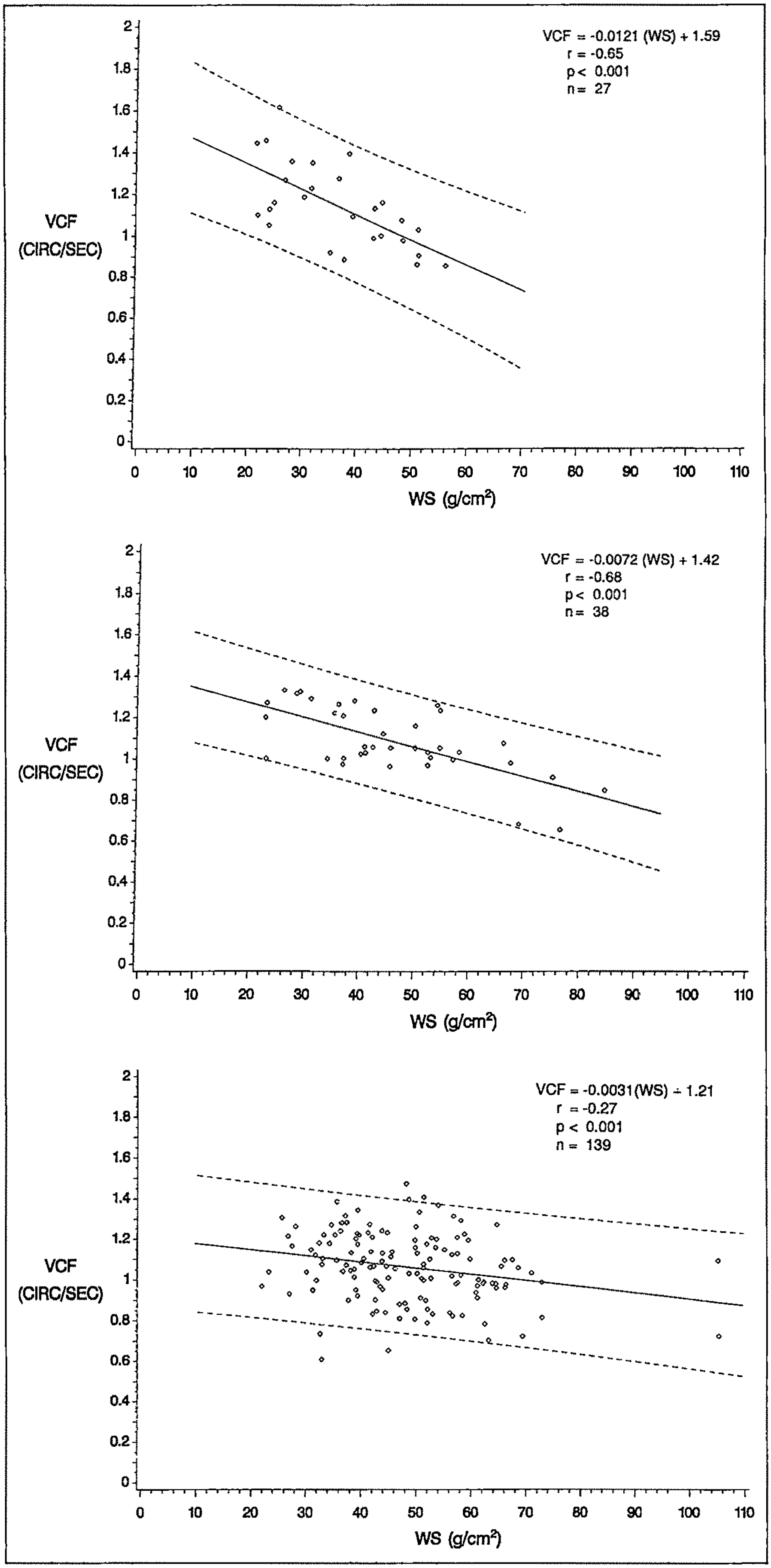

**FIGURE 1. The relation of heart rate–corrected velocity of circumferential (CIRC) fiber shortening (VCF) to end-systolic meridional wall stress (WS) in group 1 (<6 months old) (top), group 2 (>6 months old, <3 years old) *(middle)*, and group 3 (>3 years old) *(bottom)*. *Solid line* is the mean regression line; *dashed lines* are the 95% confidence limits. The regression equation, correlation coefficient, and p value are also shown for each group.**

(aged <6 months) than in group 3 (aged >3 years) ($p < 0.05$). Indexed left ventricular mass was significantly higher in group 3 than in the younger groups ($p < 0.05$).

**Velocity of circumferential fiber shortening to wall stress relation:** Reproducibility analysis showed that only 1 of the 44 repeat paired data points (VCF, WS) resulted in a difference in classification of contractile state. All other pairs were concordant.

The data points, mean regression line and 95% confidence limits for each of the 3 groups are shown in Figure 1. There was a significant main effect of WS on VCF in each group ($p < 0.001$). WS was related to VCF in an inverse linear fashion. The final model derived from the analysis of covariance was: Model VCF = WS + (AGRP) + (AGRP)(WS) where AGRP = patients age group. In addition, there were significant differences in the slopes and y-intercepts between groups 1 and 3 ($p < 0.01$) and between groups 2 and 3 ($p < 0.05$). With increasing age, the slope and y-intercept decreased (Figure 2). There was also a lower correlation coefficient between VCF and WS with age.

There was no relation between gender and fiber shortening. The slopes and y-intercepts for male patients within each group were not statistically different from those of the female patients.

## DISCUSSION

Colan et al[5] demonstrated that the VCF to WS relation in a subgroup of 30 children (3 to 18 years old) did not differ significantly from that in adults. Likewise, Franklin et al[15] studied 44 children (2 to 13 years old) and reported similar results. The parameters of the relation in the patients of these 2 studies are almost identical to that of the older children (group 3) in our study. Preliminary data by Colan et al suggest that the y-intercept of the relation is higher and the slope is no different in patients <6 months old than in those >6 months old. Our study would not support this contention. There is an increase in both slope and y-intercept in the younger patients, so that the youngest patients have the steepest slope and the highest y-intercept (Figure 2). The older the patients, the more flat the slope and the lower the y-intercept becomes so that a "family of relationships" related to age seems to prevail.

It is interesting to speculate why the relation of VCF to WS exhibits age dependence during the first years of life. Research on lambs has demonstrated significant differences in preload reserve and basal contractile state between the young and adult lamb hearts. Investigators have shown that the young myocardium has less preload reserve (i.e., it generates less force at any given preload) than the adult myocardium.[9,16] Other studies of lambs suggest that the newborn lamb operates at a higher contractile state than the adult lamb.[7-9,16,17] Our study would bear this out and also suggests that the younger left ventricle has a higher basal inotropic state at low afterload (WS). In addition, the left ventricle in young patients tolerates higher afterload less well because shortening is depressed more than in older children. Also, in the younger children, VCF was much more dependent on afterload. A similar result has been found in lambs. Romero and Friedman[6] demonstrated that VCF decreased to significantly lower levels in response to increased arterial pressure in young lambs compared with older lambs. They concluded that in the young lamb, shortening was more highly dependent on afterload, that there was limited ability to alter peripheral vascular resistance, and that a mismatch between inotropic state and afterload existed.

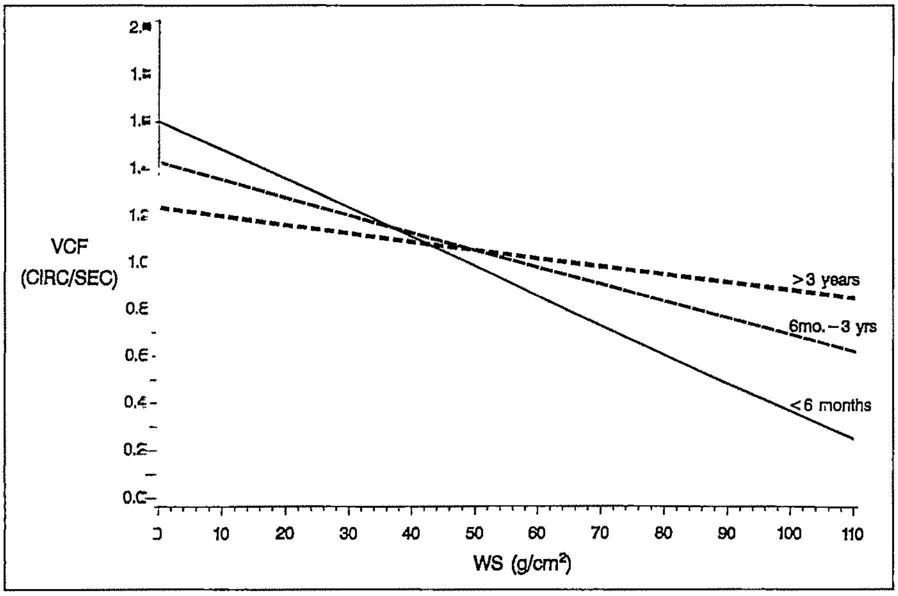

**FIGURE 2. The mean regression lines for the heart rate–corrected velocity of circumferential (CIRC) fiber shortening (VCF) and left ventricular end-systolic meridional wall stress (WS) in group 1 *(solid line)*, group 2 *(dashed line)* and group 3 *(bold, dashed line)*. With increasing age group, the regression line had a more shallow slope and lower y-intercept.**

Other investigators have also demonstrated increased sensitivity to afterload and impaired shortening at higher levels of afterload in the newborn compared with the adult lamb.[17,18] Our data suggest that similar conditions exist in the human infant.

It is interesting to note that mass indexed for body surface area increased between groups 1 and 2 and between groups 2 and 3. The latter difference was statistically significant ($p < 0.05$). It may be that mass must increase even relative to body size in order for VCF to be less dependent on afterload.

Our results demonstrate that the VCF to WS relation is reproducible over time. The relation is age-dependent in the first years of life. It has no relation to gender. Therefore, the age dependence of the VCF to WS relation must be taken into account when assessing contractile state.

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# Sudden Unexpected Death in Persons <40 Years of Age

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**This study retrospectively assesses the underlying causes of sudden unexpected death and the occurrence of prodromal symptoms in 162 subjects (aged 9 to 39 years) over a 10-year period (1976 to 1985). Underlying cardiac diseases accounted for sudden death in 73% and noncardiac causes in 15% of subjects. In 12% of subjects, the causes were unidentifiable. Myocarditis (22%), hypertrophic cardiomyopathy (22%) and conduction system abnormalities (13%) were the major causes in 32 subjects aged <20 years. Major causes of 46 deaths in subjects 20 to 29 years were atherosclerotic coronary artery disease (24%), myocarditis (22%) and hypertrophic cardiomyopathy (13%). The largest number of deaths in 84 subjects aged ≥30 years was attributed to coronary artery disease (58%), followed by myocarditis (11%). Among noncardiac causes of sudden death, intracranial hemorrhage was the most frequent (5%), followed by infectious disease (4%). Prodromal symptoms were reported by 54% of subjects; most frequent were chest pain (25%) in subjects aged ≥20 years, and dizziness (16%) in those aged <20. Sudden death, which occurred during routine daily activity in 49% and during sleep in 23% of subjects, was related to physical exercise in 23% and emotional upset in 6%. Sudden unexpected death in the young is still an unresolved medical problem. The early recognition of prodromal symptoms could be crucial in the prevention of sudden death, specifically when exercise-related.**

**(Am J Cardiol 1991;68:1388–1392)**

Sudden unexpected death in young persons is seldom encountered. The occurrence of this phenomenon in presumably healthy young men or women is highly dramatic and arouses the concern of the medical profession and of society as a whole. Anecdotal reports provide the main source of available information. Relatively few large scale studies have been conducted[1-10]; those examining young adults have mostly been concerned with military populations.[5-9] Our main objective was to investigate the phenomenon of sudden death among young persons in the general population. The occurrence of prodromal symptoms was thoroughly investigated.

## METHODS

**Study population:** It is obligatory for all deaths of undetermined cause in Israel to be investigated at the Institute of Forensic Medicine in Tel Aviv. All death records for the period 1976 to 1985 were retrospectively examined. All subjects aged 9 to 39 years who died suddenly and unexpectedly were included in the study. Sudden death was defined as death resulting from natural causes and occurring within 24 hours of onset of terminal symptoms or signs.[11] Deaths related to trauma or to previously diagnosed underlying diseases, such as asthma, epilepsy, chronic renal failure, and coronary artery or congenital heart disease, were excluded, as were sudden deaths in specific patient populations (e.g., institutionalized retardates, alcoholics and drug addicts). One hundred and ninety-eight subjects met the aforementioned criteria for sudden unexpected death. Of 198 subjects, autopsy was performed in 162 (82%) who constituted the study population. Sociodemographic variables did not differ among subjects who underwent autopsy and those who did not. There were 134 (83%) men and 28 (17%) women (ratio 5:1). Subjects were grouped by age, as follows: 32 (20%) — 9 to 19 years; 46 (28%) — 20 to 29 years; and 84 (52%) — 30 to 39 years. One hundred and forty-six subjects (90%) died 0 to 6 hours after onset of a change in clinical state, and 16 (10%) died 6 to 24 hours later.

**Data collection:** Data on sociodemographic background, circumstances of death, eyewitness accounts, prodromal symptoms and autopsy results were extracted from files at the Institute and keyed into the computer.

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**Autopsy:** All 162 autopsies were performed at the institute by 7 experts in pathology and forensic sciences. The routine protocol included a systematic examination of the heart, and an assessment of the thickness of the free walls of both ventricles, as well as of the interventricular septum. The major coronary arteries and the secondary branches were dissected mechanically. Narrowing of >50% was regarded as evidence of arteriosclerotic coronary artery disease. Histological examinations of the myocardium, the coronary arteries and serial sections of the conduction system were performed in each case. Myocarditis was diagnosed when focal or diffuse infiltration of mononuclear cells and neutrophils, together with myocytolysis or patchy myocardial necrosis and interstitial edema, were detected.[12] Hypertrophic cardiomyopathy was diagnosed when the thickness of the anterior wall of the left ventricle measured >16 mm and when there was disproportionate hypertrophy of the interventricular septum, as well as disarray of hypertrophied myofibers with extensive or perivascular fibrosis, on microscopic examination.[12] Conduction system disease was determined by focal disruption or fibrous tissue replacement, as well as acute or chronic inflammatory disease of atrioventricular nodes, His bundle or bundle branches.[12]

**Prodromal symptoms:** We carefully reviewed the occurrence of prodromal symptoms, defined as any change from normal health status considered noteworthy by the subject and reported to his family, friends or medical authorities.[3,13]

**Statistical analysis:** Chi-square tests were used to examine differences between groups; p values <0.05 were considered significant.

**TABLE I** Causes of Sudden Unexpected Death—Distribution by Age Group

| Causes of Death | <20 Years (%) | 20–29 Years (%) | ≥30 Years (%) |
|---|---|---|---|
| Cardiac | 21 (66) | 35 (76) | 62 (74) |
| Atherosclerotic coronary artery disease | 0 (0) | 11 (24) | 49 (58)* |
| Myocarditis | 7 (22) | 10 (22) | 9 (11) |
| Hypertrophic cardiomyopathy | 7 (22) | 6 (13) | 2 (2) |
| Dilated cardiomyopathy | 1 (3) | 2 (4) | 1 (1) |
| Endocardial fibroelastosis | 2 (6) | 0 (0) | 0 (0) |
| Conduction system abnormalities† | 4 (13) | 2 (4) | 0 (0) |
| Aortic stenosis | 0 (0) | 1 (2) | 0 (0) |
| Aortic regurgitation | 0 (0) | 0 (0) | 1 (1) |
| Congenital coronary anomaly‡ | 0 (0) | 1 (2) | 0 (0) |
| Coronary vasculitis | 0 (0) | 1 (2) | 0 (0) |
| Myocardial fibrosis | 0 (0) | 1 (2) | 0 (0) |
| Noncardiac | 8 (25) | 6 (13) | 11 (13) |
| Intracranial hemorrhage | 3 (9) | 3 (7) | 2 (2) |
| Heat stroke | 3 (9) | 0 (0) | 1 (1) |
| Respiratory tract infection | 1 (3) | 1 (2) | 2 (2) |
| Meningococcal meningitis | 1 (3) | 0 (0) | 0 (0) |
| Pneumococcal sepsis | 0 (0) | 1 (2) | 0 (0) |
| Hemorrhage due to extrauterine pregnancy | 0 (0) | 0 (0) | 2 (2) |
| Brain tumor§ | 0 (0) | 0 (0) | 2 (2) |
| Pulmonary embolism | 0 (0) | 1 (2) | 0 (0) |
| Rupture of aortic aneurysm | 0 (0) | 0 (0) | 1 (1) |
| Fatty liver | 0 (0) | 0 (0) | 1 (1) |
| Unidentifiable | 3 (9) | 5 (11) | 11 (13) |
| Total | 32 (100) | 46 (100) | 84 (100) |

*$p < 0.001$.

†Focal fibrosis in 4 subjects, and presence of inflammatory cells along the His bundle in 2. Mitral valve prolapse was found in 2 of 6 subjects.

‡Anomalous origin of the left coronary artery from the right sinus of Valsalva.

§Meningioma, astrocytoma (1 subject each).

## RESULTS

**Causes of sudden death:** Underlying cardiac diseases accounted for 118 of 162 (73%) deaths. Noncardiac etiologies were identified in 25 deaths (15%). In the remaining 19 deaths (12%), the cause was unidentifiable. Causes of sudden death in the 3 age groups are listed in Table I. Rates of cardiac, noncardiac and unidentifiable causes did not differ significantly, although individual causes accounted for some differences. Myocarditis, hypertrophic cardiomyopathy and conduction system abnormalities were the major underlying causes in subjects aged <20 years (Table I). In subjects aged ≥30 years, coronary artery disease was the most frequent cause, followed by myocarditis. Hypertrophic cardiomyopathy was infrequent. In the 20- to 29-year-old age group, coronary artery disease and myocarditis were the most frequent causes, followed by hypertrophic cardiomyopathy (Table I).

Pathologic evidence for acute myocardial infarction was found in 32 of 60 (53%) subjects with coronary artery disease who died suddenly and unexpectedly; a recent thrombus was present in 28 of the 32 (87%). One-vessel coronary artery disease was found in 33 of 60 (55%) subjects (left anterior descending coronary artery lesion: 25 of 33 [76%]), 2-vessel disease in 15 (25%), and 3-vessel disease in 12 (20%). The rate of acute myocardial infarction (8 of 11 [73%] vs 24 of 49 [49%] subjects), and presence of a recent thrombus (6 of 8 [75%] vs 22 of 24 [92%] subjects) did not differ significantly between the <30- and ≥30-year-old age groups. However, the number of coronary arteries involved differed significantly; 1-vessel disease was found in 10 of 11 (91%) and in 23 of 49 (47%) subjects aged <30 and ≥30 years, respectively ($p < 0.01$).

Intracranial hemorrhage was the most common noncardiac cause of sudden death (8 subjects [5%]). The hemorrhage was intracerebral in 4 subjects, subarachnoid in 3 and combined in 1. Circle of Willis aneurysm was identified in only 1 of 8 subjects. Glioblastoma multiform accounted for intracranial bleeding in 1 younger subject. In 6 subjects (4%), infectious dis-

**TABLE II** Prodromal Symptoms in the Major Diagnostic Groups

| Symptoms | CAD (n = 60) (%) | Myocarditis (n = 26) (%) | Hypertrophic Cardiomyopathy (n = 15) (%) | Intracranial Hemorrhage (n = 8) (%) | Conduction System Abnormalities (n = 6) (%) | Infectious Disease (n = 6) (%) | Unidentifiable Cause (n = 19) (%) |
|---|---|---|---|---|---|---|---|
| Chest pain | 22 (37) | 4 (15) | 2 (13) | 0 (0) | 0 (0) | 0 (0) | 2 (10) |
| Gastrointestinal symptoms | 5 (8) | 0 (0) | 3 (20) | 2 (25) | 0 (0) | 2 (33) | 0 (0) |
| Dyspnea | 7 (12) | 1 (4) | 1 (7) | 0 (0) | 0 (0) | 2 (33) | 0 (0) |
| General malaise | 2 (3) | 4 (15) | 1 (7) | 0 (0) | 1 (17) | 1 (17) | 2 (10) |
| Febrile illness | 1 (2) | 0 (0) | 1 (7) | 0 (0) | 0 (0) | 4 (67) | 3 (16) |
| Dizziness | 3 (5) | 1 (4) | 0 (0) | 0 (0) | 2 (33) | 1 (17) | 0 (0) |
| Headache | 1 (2) | 0 (0) | 1 (7) | 2 (25) | 1 (17) | 0 (0) | 2 (10) |
| Syncope | 1 (2) | 0 (0) | 1 (7) | 1 (12) | 0 (0) | 0 (0) | 1 (5) |
| Weakness, fatigue | 2 (3) | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Back pain | 1 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Palpitations | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (17) | 1 (17) | 0 (0) |
| Total number of subjects who reported prodromal symptoms* | 31 (52) | 9 (35) | 9 (60) | 4 (50) | 3 (50) | 5 (83) | 9 (47) |

*Several symptoms were reported by some subjects.
CAD = atherosclerotic coronary artery disease.

ease, mostly respiratory tract infection, was the cause (Table I).

Cardiac causes of sudden death were more frequent in men (105 of 134 [78%]) than in women (13 of 28 [46%]; $p < 0.01$). Noncardiac causes were more often encountered in women (11 of 28 [39%]) than in men (14 of 134 [10%]; $p < 0.01$). A significantly higher incidence of coronary artery disease in men (56 of 134 [42%]) than in women (4 of 28 [14%]; $p < 0.01$) accounted for the difference between the sexes in cardiac causes. The more frequent noncardiac causes in women included: intracranial hemorrhage (5 women [18%] vs 3 men [2%]); brain tumor (2 women [14%] vs 0 men [0%]); and acute bleeding (2 women [14%] vs 0 men [0%]; $p < 0.01$).

**Prodromal symptoms:** Prodromal symptoms were reported by 87 of 162 (54%) subjects. The incidence of these symptoms did not differ significantly between men and women (74 of 134 [55%] vs 13 of 28 [46%]), nor among the 3 age groups (18 of 32 [56%], 26 of 46 [57%], and 43 of 84 [51%], in subjects aged <20, 20 to 29, and ≥30 years, respectively). Chest pain was most frequent in subjects aged ≥20 years, and was relatively infrequent in those aged <20 years (32 of 130 [25%] vs 2 of 32 [6%]; $p < 0.05$). Dizziness was most widely reported by subjects aged <20 years, and was relatively infrequent in those aged ≥20 years (5 of 32 [16%] vs 3 of 130 [2%]; $p < 0.01$). Syncope, reported by 2 to 4% of subjects, was infrequent in all 3 age groups.

Before sudden death 63 of 87 subjects reported 1 symptom, 19 reported 2 symptoms, 3 reported 3 symptoms and 2 reported 4 symptoms. Fifty-four of 87 (62%) subjects reported symptoms within 24 hours, 15 (17%) within 1 to 7 days, 8 (9%) within 8 to 30 days, and 10 (12%) >30 days before sudden death.

Prodromal symptoms were reported by 50 to 60% of subjects in most major diagnostic groups (Table II). The symptoms were somewhat less frequent (35%) in myocarditis, and more frequent (83%) among deaths resulting from infectious disease (Table II). However, these differences were not significant. Table II shows distribution of prodromal symptoms in the major diagnostic groups. Because of the small number of subjects it was difficult to establish a relation between prodromal symptoms and underlying causes of sudden death, with the exception of chest pain, which was more frequent in coronary artery disease than in death from other causes (22 of 60 [37%] and 12 of 102 [12%], respectively; $p < 0.01$).

**Circumstances of sudden death:** The circumstances were established in 137 of 162 (85%) subjects; 67 (49%) died during routine daily activity, 31 (23%) during sleep, 31 (23%) had exercise-related deaths, and 8 (6%) had deaths related to emotional upset. Death during routine daily activity was more frequent in subjects aged ≥30 years (62 vs 35% in subjects aged <30 years; $p < 0.01$); exercise-related sudden death was more frequent in the younger than in the older subjects (31 vs 14% of <30- and ≥30-year-old age groups, respectively; $p < 0.05$).

The circumstances did not differ significantly in deaths from cardiac, noncardiac or unidentifiable causes (Table III); however, individual causes accounted for some differences. Sudden death during sleep was more often encountered in myocarditis (9 of 22 [41%] vs 22 of 115 [19%] subjects whose deaths were attributable to other causes; $p < 0.05$). Exercise-related sudden death was significantly more frequent in cardiomyopathy (hypertrophic, dilated or endocardial fibroelastosis) (8 of 20 [40%] vs 23 of 117 [20%] deaths from other causes; $p < 0.05$). Deaths resulting from heatstroke were exclusively exercise-related (4 of 4 [100%] vs 27 of 133 [20%] as a result of other causes; $p < 0.002$). Congenital coronary anomaly and aortic stenosis accounted for exercise-related sudden death in 1 subject each.

Prodromal symptoms were reported by 42 of 67 (63%) subjects who died during routine daily activity, 18 of 31 (58%) whose deaths were exercise-related, 15 of 31 (48%) who died during sleep, and 4 of 8 (50%) who died after an emotional upset. No statistically significant differences were demonstrated among these groups. Syncope was exercise-related in 4 of 5 subjects. Otherwise, no relation was established between prodromal symptoms and circumstances of death.

## DISCUSSION

This study demonstrates the distribution of causes of sudden death, and the incidence of prodromal symptoms in young persons. We believe that the study population of 162 subjects (aged 9 to 39 years) who died suddenly and unexpectedly is among the largest series investigated.

Cardiac causes accounted for sudden death in most subjects. Our findings concur with various other studies,[1,3] but lack agreement with others.[2,5,8] Neuspiel and Kuller[2] demonstrated that the incidence of cardiac causes of sudden death increases with age (children 20%, adolescents 30%, young adults 40%, aged $\geq 40$ years 75%). In our study, the incidence was >65% in the 3 age groups (aged <20, 20 to 29, and $\geq 30$ years) and was remarkably lower in women.

Coronary artery disease was the major cause of death in subjects aged $\geq 30$ years (58%), and the most frequent cause in the 20- to 29-year-old age group (24%). In previous studies, the incidence of this disease among subjects aged 18 to 39 years who died suddenly was approximately 30%.[4,5,10] A higher rate (76%) was reported among British soldiers[7] whose ages ranged from 18 to 55 years.

Myocarditis was a major cause of sudden death, accounting for 16% in all subjects and for 11 to 22% in the 3 age groups. Lower prevalence rates (1 to 7%) have been recorded previously.[1,2,5,7,8,10] However, a higher prevalence (17%), compatible with our data, was found in another recent study.[14] Lack of uniform diagnostic criteria may account for this inconsistency.[14]

Hypertrophic cardiomyopathy accounted for sudden death in 17% of subjects aged <30 years, thus supporting the assumption that this disease is a significant precursor of sudden death in the young.[1,13,15,16] Right ventricular cardiomyopathy, which has recently been associated with sudden death in young people,[17] was absent in our subjects. Our report supports that of Bharati & Lev,[18] which showed that congenital abnormalities of the conduction system play a significant role in precipitating sudden death in the young. We also endorse the hypothesis that mitral valve prolapse is an infrequent cause of sudden death.[13]

**TABLE III** Circumstances of Sudden Unexpected Death—Distribution by Underlying Causes

| Circumstances of Death | Cardiac (n = 100) (%) | Noncardiac (n = 21) (%) | Unidentifiable (n = 16) (%) |
|---|---|---|---|
| Routine daily activity | 47 (47) | 11 (52) | 9 (56) |
| Physical exercise | 23 (23) | 5 (24) | 3 (19) |
| Sleep | 25 (25) | 4 (19) | 2 (12) |
| Emotional upset | 5 (5) | 1 (5) | 2 (12) |

Congenital coronary anomalies, particularly anomalous origin of the left coronary artery from the right sinus of Valsalva, have been increasingly reported as the cause of sudden death in the young.[13,19-21] These deaths are usually exercise-related and associated with almost total occlusion of the anomalous artery during exercise.[13,19,20] However, our study shows that congenital coronary anomalies should be viewed as an infrequent cause of sudden death in the young. The higher incidence previously reported[21] may derive from a growing interest in and a tendency to publicize such cases. This study reviews a 10-year period and is believed to include all sudden deaths in our young population; thus, it probably reflects the accurate incidence attributable to congenital coronary anomalies.

The low incidence of sudden death during sleep[22] was not confirmed; subjects who died during routine daily activity outnumbered by a ratio of only 2:1 deaths that occurred during sleep. Considering the actual hours usually given to both activities, this finding does not indicate reduced risk for sudden death during sleep. Exercise-related sudden death occurred in 23% of subjects, and a similar rate (15 to 30%) was observed among young subjects, mostly in military populations.[5-8] Sudden death associated with acute emotional upset has lately become a subject of increasing interest.[23] Data on population-based incidence rates are lacking; therefore, comparison with our rate of 6% was not feasible.

The incidence of prodromal symptoms reported by 54% of subjects did not differ significantly among the various age, sex and diagnostic groups, nor in differing death circumstances. Previous studies demonstrated a 75 to 80% incidence of prodromal symptoms among older persons who died of coronary artery disease,[24] and a substantially lower rate (25%) among the young.[3] The major importance of syncope has been noted in studies mainly concerned with athletic or military populations and with exercise-related sudden death.[3,13,25] In our study, syncope was reported by just 3% of subjects. The most frequent prodromal symptoms were chest pain and dizziness in subjects aged ≥20 and <20 years, respectively.

There is a need for early evaluation of prodromal symptoms in prevention of sudden death as indicated by our data. Although prevention of sudden death in the young is a major issue, the extent to which this can be achieved is questionable. A more practical objective is the prevention of exercise-related sudden death[21,26] in which the recognition of prodromal symptoms could be crucial.

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# The Mystery of Nitrate Resistance

Jonathan Abrams, MD

Although nitrate tolerance is a well-recognized phenomenon in angina pectoris and congestive heart failure (CHF), the problem of primary resistance or nonresponsiveness to nitroglycerin (NTG) and the organic nitrates is not widely recognized. In this issue of the Journal, Varriale and colleagues have replicated the results of previous clinical investigations that have documented nitrate resistance in patients with severe CHF.[1-9] In addition, the authors have again demonstrated that a high systemic venous pressure (manifest by a mean right atrial pressure of 17 ± 4 mm Hg) or gross-dependent edema, or both, are variables that predict an increased likelihood of nitrate resistance.[1,2,8,9] The current report, while devoid of data regarding the underlying mechanisms of nitrate resistance, should serve to remind clinicians that resistance is a potential problem in subjects with heart failure treated with nitrates as adjunctive therapy.

The study demonstrated that a substantial proportion of sick (class III to IV) patients with CHF may not respond to intravenous NTG with a desirable decrease in left or right ventricular preload, despite administration of very large doses. Magrini and Niarchos,[2] Armstrong,[1,7] Elkayam,[3,6] Kulick[8] and their coworkers previously documented this phenomenon in similar patient cohorts. Furthermore, this study mirrors the earlier Italian experience demonstrating that vigorous diuretic therapy restores nitrate responsiveness,[2] although the mechanism(s) is unclear.

These observations are important for clinicians. Nitrate therapy is effective in patients with CHF, and, in class III to IV patients, can improve the signs and symptoms of heart failure with substantial hemodynamic benefit. Furthermore, in combination with hydralazine, isosorbide dinitrate has been shown to reduce mortality in patients with class II to III CHF in 2 randomized trials.[10,11] Thus, it is essential to administer organic nitrates in an effective manner. The data of Varriale et al, when put into context with earlier trials, indicate that severely ill subjects with CHF, typically with biventricular failure, require particular vigilance in documenting a nitrate response.

For the investigator, this study raises important questions about the pathophysiology of nitrate resistance. Future well-designed trials of nitrate resistance are indicated to establish the true prevalence of resistance, provide a better understanding of the neurohumoral interrelations, and carefully assess regional blood volume, venous capacitance and arterial vascular resistance.

**Which patients are nitrate resistant?** This study demonstrates the benefits that can be derived when individual patient data are presented along with group data in the assessment of clinical responses to a particular therapy. Most studies of vasodilator therapy in CHF report mean group data. Thus, the problem of individual subjects with poor response to a therapy may not be obvious. Many studies of nitrates in heart failure do not report resistance as a problem, despite the use of high doses of NTG or isosorbide dinitrate. Furthermore, the criteria used to define nitrate resistance vary from study to study. Finally, increasing the nitrate dose can diminish the apparent frequency of the problem in the same patient cohort.[1,3,4,5,8,9] The prevalence of nitrate resistance in a variety of investigations documenting this problem ranges from 12.5[4] to 50%.[3,7] Although New York Heart Association class or ejection fractions are not always provided in these reports, hemodynamic monitoring suggests a comparable degree of elevation of left and right ventricular filling pressures in the various patient cohorts.[1-9] Subjects with systolic or diastolic dysfunction, or both, are included in some studies; it is unknown if nitrate resistance is a common occurrence in patients with the CHF syndrome and intact left ventricular function (isolated diastolic dysfunction) because data are not available to allow such analysis.

It is clear that nitrate resistance is present only in severe CHF, often but not always including subjects with peripheral edema.[1-8] In the present study and in some other reports (but not all), the presence of an elevated right atrial pressure, as well as dependent edema, have been found to be helpful in predicting the likelihood of nitrate resistance.[1,2,8,9] Edema as a "risk factor" is specifically cited in a minority of studies, and

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was apparently not present in the reported largest cohort.[6]

It is unclear if nitrate resistance is an important problem in the therapy of angina pectoris. Most subjects with chest discomfort due to coronary atherosclerosis predictably respond to sublingual NTG. Only group data are generally reported in angina protocols, and NTG "nonresponders" are often excluded from the actual studies. Nevertheless, my impression is that patients with angina pectoris rarely experience true nitrate resistance, and almost all patients obtain relief from ischemic pain with rapid-acting NTG formulations within 4 to 5 minutes.

**What is the basis for nitrate resistance?** Varriale et al propose a variety of possible mechanisms, as do other investigators[,5,8,9] which include: mechanical compression of the peripheral vasculature or surrounding tissue, or both; salt and water infiltration of the blood vessels; an overly engorged and noncompliant venous circulation, presumably unable to further dilate; decreased bioavailability of delivered drug; altered nitrate metabolism (sulfhydryl depletion) within the vascular smooth muscle cell; and excessive neurohumoral activation with marked systemic arterial (and venous) vasoconstriction. None of these factors have been systematically investigated. Several studies have measured plasma nitrate levels in resistant subjects, and have demonstrated adequate drug concentrations.[1,7,9]

Neurohumoral activation is a particularly attractive candidate. The hypothesis is that subjects who are resistant to nitrates have more intense systemic venous and arterial constriction due to excessive elevations of catecholamines, angiotensin II, and other bioactive substances, such as renin or arginine vasopressin. Furthermore, the recent documentation that plasma endothelin levels are increased in CHF[12] suggest that endogenous endothelial vasodilator activity is likely to be attenuated in CHF, and that endogenous vasoconstrictor substances are dominant. NTG is considered to be an exogenous endothelial-relaxing factor,[13] and works in the absence of normal endothelial function; therefore, endothelial dysfunction, per se, is not a plausible explanation for nitrate resistance, because NTG is considered to be actually more potent in the presence of abnormal endothelial function.[14]

Extrapolation of data from Elkayam et al do not suggest that neurohumoral activation is greater in nitrate-resistant patients; these workers measured plasma renin, epinephrine and norepinephrine before and during a 24-hour infusion of intravenous NTG, and were unable to demonstrate any differences in patients with CHF who did or did not subsequently develop nitrate tolerance.[5] However, no measurements of renin or catecholamines were reported in patients (5 of 40) who did not respond to the initial intravenous NTG infusion. Thus, rapid and excessive elevation of plasma and tissue levels of various vasoconstrictor substances (norepinephrine, epinephrine, angiotensin II, endothelin and arginine vasopressin) remain a possible mechanism for nitrate resistance.

**Is nitrate resistance an exaggerated variant of nitrate tolerance?** Many studies have documented a remarkably rapid onset of tolerance or attenuation to nitrates, beginning within several hours of administration, and reaching a significant degree of vascular hyporesponsiveness within 24 hours.[4–6,9,15–19] It is attractive to view nitrate resistance as a compressed model of nitrate tolerance, manifesting an immediate rather than delayed failure of the vasculature to respond to organic nitrates. Tolerance in general, and in CHF in particular, is a complex phenomenon, with multiple causation. The sulfhydryl or cysteine depletion theory remains an important concept underlying attenuation to nitrate action. Armstrong[1] and Elkayam[6] and their co-workers suggested rapid intracellular sulfhydryl depletion as a possible mechanism for resistance; some studies,[16] but not all,[15] have demonstrated reversal of nitrate tolerance in CHF with sulfhydryl donors in patients given high doses of intravenous NTG. Investigations using prior or simultaneous administration of sulfhydryl donors, such as methionine or N-acetylcysteine, could be designed to answer this question. I believe that sulfhydryl depletion or unavailability is an unlikely single cause for nitrate resistance.

Two recent studies have documented remarkably rapid alterations in plasma volume and onset of neurohumoral activation in patients with CHF[15] and in normal subjects[26] with induced NTG tolerance. Dupuis et al[15] confirmed a plasma volume shift within the first hour of NTG therapy, as well as increases in arginine vasopressin and epinephrine in several subjects within a similar time interval. Parker et al[20] demonstrated a prompt decrease in hematocrit and increase in weight, consistent with salt and water retention due to documented neurohormonal activation after transdermal NTG application. These changes occur quite rapidly. Thus, it is conceivable that extremely fast shifts of plasma volume or neurohumoral activation, or both, could play a role in nitrate resistance.

**Elevated right atrial pressure and edema:** Finally, it may be useful to speculate on the significance of the elevation in right atrial pressure and the presence of peripheral edema as markers for nitrate resistance. Both are indicative of severe biventricular heart failure and marked engorgement of the venous capacitance system. Tissue or vascular compression due to interstitial and cellular edema could play a role in the hyporesponsiveness of the venous system to nitrates in the presence of resistance. Nitrate efficacy in CHF is modulated by both venous and arterial vasodilation. Decreases in right or left ventricular filling pressures are presumed to be due to regional and systemic venodilation. After NTG administration, the circulating blood volume is redistributed away from the heart and lungs to the mesenteric and splanchnic circulations and to the legs and arms.[21–23] A high right atrial pressure appears to be a marker for an impaired ability of the venous bed(s) to vasodilate, probably due to a combination of mechanical (high tissue and intravascular pressure) and vasoconstrictor forces. Reduction of tissue edema with diuretics may act mechanically on the blood vessels, but is unlikely to reduce vasoconstrictor forces. Perhaps the efficacy of diuretics in restoring nitrate responsiveness indicates that neurohumoral mechanisms are less important. Elkayam,[4,6] Kulick,[8] Packer[9] and their coworkers showed that increasing the nitrate dose can usually overcome nitrate resistance, although this may require huge doses, and not all subjects will respond. Resistance is to some degree a dose-response problem; larger NTG doses are usually required in patients with CHF, and conventional nitrate dosing may not work in the sickest patients.

An elevated right atrial pressure has also been associated with resistance to other vasodilators in CHF, including hydralazine[24] and captopril.[25] Thus, the problem of tolerance to vasodilators may be relatively common in patients with severe biventricular failure, perhaps helping to explain why these subjects often do poorly once refractory CHF has appeared, especially those with peripheral edema. It is possible that a very high systemic venous pressure is related to decreased renal function and blood flow, which might worsen after administration of a potent vasodilator,[26] increasing vasoconstrictor forces. This could help explain the preliminary report that hydralazine prevented nitrate tolerance in a rat model of CHF[27]; it was postulated that renal blood flow was preserved by the co-administration of hydralazine. In any case, the clinical paradox is that patients most in need of vasodilator therapy may be least likely to respond.

**Conclusion:** Clinicians need to be more aware of the problem of nitrate resistance. Careful assessment of patients with CHF with physical examination and chest x-ray can help identify those most likely to be resistant. Thus, a high jugular venous pressure and the presence of peripheral edema are good indicators that nitrate resistance is likely to be present (perhaps as high as 50% in some class III to IV subjects). A poor clinical response may mandate a pulmonary artery catheter, as suggested by Varriale, although vigorous diuresis should first be performed in edematous patients. Such an approach should optimize nitrate therapy in these seriously ill patients.

For investigators, nitrate resistance remains an enigma that deserves further attention. I believe that carefully designed trials would unravel the mysteries of nitrate resistance and provide important new clues as to the mechanisms of nitrate vasodilatation and nitrate tolerance.

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# Reproducibility and Relation to the Degree of Myocardial Ischemia of Postexercise Electrocardiographic Changes in Stable Angina Pectoris

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In recent times, increasing attention has been paid to the recovery phase after exercise in patients with stable angina pectoris. The relation between a prolonged postexercise ST-segment depression and the degree of impairment of exercise tolerance, extent and severity of coronary artery disease, presence of collateral circulation and degree of left ventricular dysfunction has been investigated.[1-5] Little is known about the reproducibility of postexercise ST-segment changes, and few studies have investigated the possible determinants of recovery duration in individual patients; in addition most studies have focused on the possible role of body position during and after exercise[6,7] or of exercise type.[7] This study investigates the reproducibility of postexercise ST-segment changes and identifies which parameters are capable of influencing them in individual patients.

*We studied 18 patients (16 men, 2 women), aged 53 to 66 years (mean 61 ± 4) with chronic stable angina without appreciable changes in clinical status in the previous 3 months; at the time of the study 4 patients were asymptomatic, 14 had effort angina, 7 reported a variable threshold for effort angina and 4 had occasional episodes of rest angina. All patients had positive exercise test results (horizontal or downsloping ST-segment depression* $\geq 1$ *mm [1 mm = 0.1 mV]), angiographically documented coronary artery disease (internal diameter reduction* $\geq 70\%$ *of 1 vessel in 11 patients, of 2 vessels in 5 patients and of 3 vessels in 2 patients) and no previous myocardial infarction. Duration of symptoms ranged from 0.3 to 10 years (mean 2.4 ± 2.4). All patients were in sinus rhythm and none had evidence of heart failure, cardiomyopathy or valvular disease. All patients had a normal ST-segment level at rest and none were taking digitalis. Each patient had undergone* $\geq 2$ *treadmill exercise tests with the modified Bruce protocol and was familiar with the test environment before study entry. Written informed consent was obtained from all patients. After antianginal drug withdrawal (*$\geq 2$ *days for nitrates and calcium entry blocking agents and* $\geq 4$ *days for* $\beta$*-blocking agents) all patients underwent 2 exercise tests in consecutive days. Exercise tests were performed between 0900 and 1200 hours; the room temperature was kept at 20 to 24°C. Patients were requested to abstain from smoking for* $\geq 3$ *hours and from eating xanthine-containing food and drinks for* $\geq 12$ *hours before the tests. Within a week, all patients performed an exercise test immediately after the administration of 0.5 mg of sublingual nitroglycerin; the effects of nitroglycerin were evaluated by comparison with the second exercise test without therapy. The modified Bruce protocol was used[8]; end points were fatigue, progressive angina and ST-segment depression* $\geq 3$ *mm. After exercise, patients were asked to recover in the sitting position. Twelve-lead electrocardiograms and blood pressure monitoring were recorded during the control period and at 1-minute intervals during exercise and for* $\geq 6$ *minutes during recovery. The level of the ST segment, 60 ms after the J point, was calculated in all 12 leads by a computer-assisted system (Burdick ExTol 700) measuring the ST-segment level with a precision of 0.1 mm. The electrocardiographic lead showing the greatest ST-segment depression was selected for analysis. In each test recovery duration was calculated as the time from peak exercise to the end of recovery (point at which the ST segment returns to baseline level ± 0.2 mm).[9] Time, heart rate and heart rate–systolic blood pressure product (rate-pressure product) at 1 mm of ST-segment depression and at peak exercise were also measured. Continuous data are presented as mean ± standard deviation. Statistical analysis was performed by Student's* t *test for paired and unpaired data, as appropriate. Differences between proportions were analyzed with chi-square or Fisher exact test, as appropriate. Correlations between parametric data were performed by linear regression analysis; correlations between parametric and nonparametric data were performed using the Spearman rank correlation coefficient. A p value* $<0.05$ *was considered statistically significant.*

*Exercise parameters during repeat testing without therapy showed a high degree of reproducibility. All tests were positive for ST-segment depression in both occasions; very high correlation coefficients were obtained for heart rate at 1 mm ST-segment depression (113 ± 35 vs 114 ± 34 beats/min,* $r = 0.95$, $p < 0.0001$*), heart rate at peak exercise (128 ± 24 vs 129 ± 24 beats/min,* $r = 0.94$, $p < 0.0001$*), rate-pressure*

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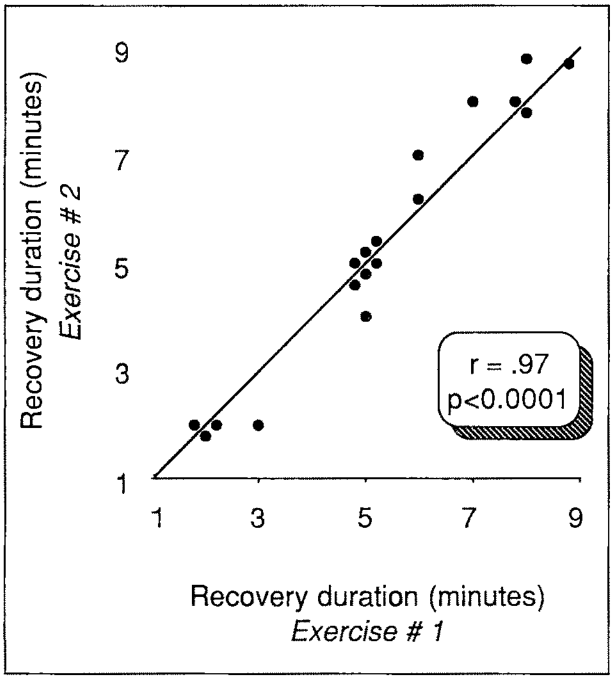

**FIGURE 1. Reproducibility of recovery duration during repeat exercise testing without therapy. *Line* across the *graph* is the identity line.**

*product at 1 mm ST-segment depression (187 ± 73 vs 189 ± 75 beats/min · mm Hg · $10^2$, $r = 0.96$, $p < 0.0001$), rate-pressure product at peak exercise (223 ± 65 vs 223 ± 69 beats/min · mm Hg · $10^2$, $r = 0.91$, $p < 0.0001$), and peak ST-segment depression (1.65 ± 0.45 vs 1.72 ± 0.52 mm, $r = 0.69$, $p < 0.005$). Exercise time showed a significant increase comparing the second exercise test to the first; time at 1 mm ST-segment depression increased from 385 ± 232 to 466 ± 230 seconds ($p < 0.01$) and time to peak exercise increased from 517 ± 196 to 619 ± 211 seconds ($p < 0.005$). Nevertheless exercise times both at 1 mm ST-segment depression and at peak exercise showed a very high correlation coefficient ($r = 0.89$ and $r = 0.87$, $p < 0.0001$ for both). Postexercise ST-segment changes also showed a high degree of reproducibility. Recovery duration was 5.3 ± 2.1 minutes during the first exercise test and 5.4 ± 2.4 minutes during the second, yielding a correlation coefficient of 0.97 ($p < 0.0001$) (Figure 1). It is worthwhile to observe that the points distribution in Figure 1 rules out any systematic over- or underestimation of recovery duration comparing one test with the other. Recovery duration was not related to any exercise parameter during exercise testing without therapy. In particular, no significant correlation was found between recovery duration and heart rate at 1 mm ST-segment depression ($r = 0.16$, $p$ = not significant [NS]), heart rate at peak exercise ($r = 0.15$, $p$ = NS), rate-pressure product at 1 mm ST-segment depression ($r = 0.39$, $p$ = NS), and at peak exercise ($r = 0.19$, $p$ = NS). Recovery duration was not significantly related to exercise time at 1 mm ST-segment depression and at peak exercise both during the first exercise test ($r = 0.35$, $p$ = NS; $r = 0.45$, $p = 0.06$, respectively) and during the second ($r = 0.32$, $p$ = NS; $r = 0.41$, $p$ = NS, respectively); changes in exercise time at 1 mm ST-segment depression and at peak exercise between the 2 exercise tests without treatment were not related to changes in recovery duration ($r = 0.12$ and 0.15, respectively, $p$ = NS for both). No relation was found between number of diseased vessels and recovery duration ($r = 0.34$, $p$ = NS); in particular, recovery duration was 4.9 ± 1.9 minutes in patients with 1-vessel disease compared with 6.3 ± 2.2 minutes in patients with multivessel disease. Similarly, the absolute amount of ST-segment depression did not predict the duration of recovery ($r = 0.39$, $p = 0.09$). Sublin-*

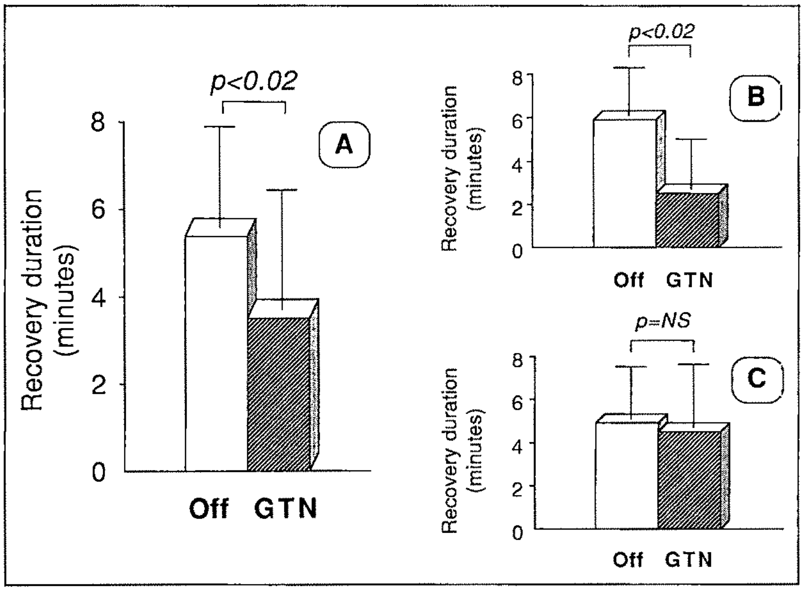

**FIGURE 2. Effects of sublingual nitroglycerin (GTN) on recovery duration in the overall population *(panel A)* and in subgroups with (group I, *panel B)* and without (group II, *panel C)* a reduction of ≥0.5 mm in maximal ST-segment depression after nitroglycerin. NS = not significant.**

*gual nitroglycerin administration resulted—on average—in a significant increase in exercise time, heart rate and rate-pressure product at 1 mm ST-segment depression (from 462 ± 218 to 531 ± 200 seconds, $p < 0.05$; from 105 ± 10 to 123 ± 17 beats/min, $p < 0.005$; from 156 ± 19 to 190 ± 35 beats/min · mm Hg · $10^2$, $p < 0.002$ respectively). Similarly a significant increase in exercise time, heart rate and rate-pressure product was observed at peak exercise (from 620 ± 217 to 709 ± 217 seconds, $p < 0.05$; from 130 ± 26 to 144 ± 24 beats/min, $p < 0.001$; from 224 ± 68 to 244 ± 56 beats/min · mm Hg · $10^2$, $p < 0.05$, respectively). Maximal ST-segment depression decreased from 1.62 ± 0.43 to 1.10 ± 0.71 mm ($p < 0.05$), becoming <1 mm (range 0.1 to 0.8 mm) in 7 patients. Recovery duration was significantly shortened after administration of sublingual nitroglycerin, decreasing from 5.4 ± 2.3 to 3.5 ± 2.7 minutes ($p < 0.02$) (Figure 2). Patients were subsequently divided into 2 groups: those with (group I, $n = 9$) and without (group II, $n = 9$) a decrease of $\geq 0.5$ mm in maximal ST-segment depression after nitroglycerin. The 2 groups were not significantly different with regard to exercise parameters without treatment or to nitroglycerin-induced changes in exercise parameters; after nitroglycerin, ST-segment depression decreased from 1.84 ± 0.42 to 0.60 ± 0.55 mm in group I patients, and was unchanged in group II patients (1.40 ± 0.35 vs 1.60 ± 0.47 mm). A significant reduction in recovery duration was only observed among group I patients (from 5.9 ± 2.2 to 2.5 ± 2.3 minutes, $p < 0.02$), whereas no significant changes in recovery duration were observed in group II (4.9 ± 2.4 vs 4.5 ± 2.9 minutes, $p = NS$) (Figure 2). Changes in recovery duration after nitroglycerin were closely related to changes in maximal ST-segment depression ($r = 0.77$, $p < 0.001$) (Figure 3). Conversely, no correlation was observed between changes in recovery duration and changes in exercise time, heart rate and rate-pressure product at 1 mm ST-segment depression ($r = 0.03$, 0.02 and 0.09, respectively; $p = NS$ for all) or changes in exercise time, heart rate and rate-pressure product at peak exercise ($r = 0.01$, 0.04 and 0.14, respectively; $p = NS$ for all).*

Our study shows that postexercise ST-segment changes are a highly reproducible parameter: in fact, comparing recovery duration during repeat exercise tests without therapy, a very high correlation coefficient was obtained. The reproducibility of exercise parameters has already been demonstrated to be good in several studies. Similar results have also been obtained in our patients, especially regarding heart rate and rate-pressure product at the ischemic threshold; exercise time was prolonged during the second exercise test, a phenomenon that can be ascribed to an already described[10] "training effect" most likely resulting from improved biomechanical efficiency. However, our study specifically addresses the issue of the reproducibility of postexercise ST-segment changes, showing that these changes are as much reproducible as the other exercise parameters. We found no relation between recovery duration and exercise time, heart rate and rate-pressure product at peak exercise, number of diseased vessels, and amount of ST-segment depression: Although a previous study suggested a trend toward a more prolonged ST-segment depression in patients with strongly positive exercise test results compared to patients with milder ST-segment changes,[11] our data are in agreement with the majority of previous studies[2–5,9] showing no association between a prolonged recovery period and more extensive coronary artery disease or markedly impaired exercise tolerance. In our study no relation was found between a prolonged recovery duration and a low ischemic threshold, in contrast to a previous report[3]: these differences are likely to be due to the relatively small number of patients enrolled in the present study and to the considerable overlap between patients with long and short recovery periods found in that study.[3] Previous studies have shown that recovery duration can be influenced by body position during or after exercise,[6,7] and not by the modalities with which the exercise is performed.[7] Our study strongly indicates that in individual patients the degree of myocardial ischemia is the principal determinant of recovery duration. Indeed, in our study changes in recovery duration were closely related to changes in the amount of ST-segment depression developing at peak exercise; similar data had also been obtained by Detry and Bruce,[12] who found decreased ST-segment depression during and after exercise after administration of sublingual nitroglycerin: however, no relation between maximal ST segment depression and recovery duration was proposed in that study. Recovery duration changes appear to be independent of changes in hemodynamic parameters; in fact no significant correlation was found between changes in recovery duration and changes in heart rate or rate-pressure product both at 1

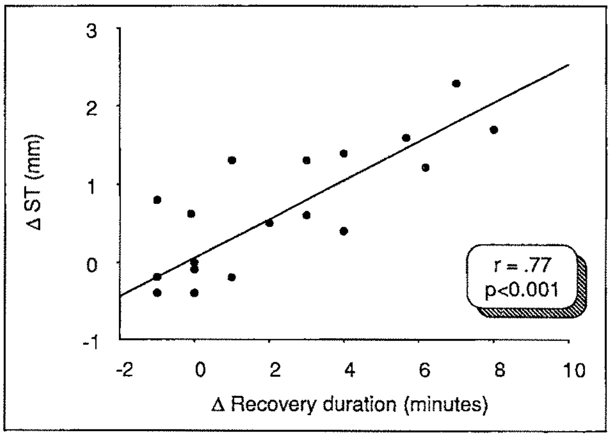

**FIGURE 3. Relation between changes (Δ) in recovery duration and changes in maximal ST-segment depression (Δ ST).**

mm ST-segment depression and at peak exercise. A limitation to this conclusion is the fact that we used nitroglycerin as a means of producing changes in exercise-induced myocardial ischemia; we cannot rule out that when administering drugs with different mechanisms of action, correlations between exercise parameters and recovery duration may be observed. In conclusion, postexercise ST-segment changes are highly reproducible. The duration of the recovery period is relatively independent of maximal ST-segment depression, exercise time and hemodynamic parameters; however, in individual patients, its changes are closely related to changes in the degree of myocardial ischemia, independently of the work load at which it occurs. Postexercise ST-segment changes are a potentially valuable parameter in evaluating interventions aimed at modifying onset and regression of exercise-induced myocardial ischemia.

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# Hemodynamic Resistance to Intravenous Nitroglycerin In Severe Congestive Heart Failure And Restored Response After Diuresis

Philip Varriale, MD, William J. David, MD, and Basil E. Chryssos, MD

A wide variety of organic nitrate preparations are often used in the management of congestive heart failure (CHF). This class of drugs exerts a vasodilatory action, predominantly on the venous capacitance vessels, that leads to a reduced ventricular filling pressure and usually without an increase in cardiac output.[1,2] Two major problems exist that deter its widespread acceptance as an effective drug in CHF: the development of tolerance and hemodynamic resistance or primary drug failure. Tolerance is responsible for the loss of hemodynamic and clinical benefits after nitrate therapy has been initiated.[3-5] An absent or feeble hemodynamic response to nitrates, a relatively common occurrence, has been reported to occur in approximately ≥50% of treated patients.[6,7] However, nitrate resistance is not always apparent when intravenous nitroglycerin is used without hemodynamic monitoring. This study was designed for 2 purposes: (1) to substantiate previously described hemodynamic and clinical correlates of CHF predictive of resistance to intravenous nitroglycerin,[6,7] and (2) to determine whether hemodynamic modification using alternate drug therapy might restore responsiveness to nitroglycerin.

*Twenty-six patients (14 men and 12 women, mean age 71 ± 12 years) with severe chronic CHF (class IV) refractory to previous drug therapy had bedside hemodynamic evaluation (Swan-Ganz catheter) and guided drug therapy. Coronary artery disease was the exclusive underlying cause of heart failure; 12 patients had associated hypertension and 9 patients had diabetes mellitus. Nine patients had edema of the dependent portion of the body including the sacrum. The left ventricular ejection fraction in 14 patients ranged from 11 to 53% (mean 32 ± 14) and all patients had cardiomegaly and marked pulmonary congestion on chest x-ray.*

*A balloon-tipped Swan-Ganz thermodilution catheter was placed into the pulmonary artery after all previous medications (digoxin, diuretics and vasodilators) were discontinued for ≥24 hours. Baseline measurements were obtained 12 hours after Swan-Ganz catheter insertion to lessen the vagaries of hemodynamic changes due to this procedure.[8] Pressures were recorded in the right atrium, pulmonary artery and pulmonary artery occlusive position. Cardiac*

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*output was determined by thermodilution from triplicate measurements. Cardiac, systemic vascular resistance and stroke volume indexes were computer-derived (Hewlett-Packard 2648A).*

*A nitroglycerin infusion was administered to all patients and increased 10 μg every 5 minutes until the wedge pressure decreased to relatively normal levels (10 to 14 mm Hg) or until a ≥30% reduction in baseline wedge pressure was obtained. Intravenous nitroglycerin was given to a maximal dose of 400 μg/min to achieve this end point or discontinued at a lower dosage because of hypotension or excessive heart rate changes. Intravenous furosemide was given to those who failed to achieve this therapeutic goal as follows: 40 mg every 6 hours (using supplemental oral potassium as required) and continued until the right atrial pressure declined to 10 mm Hg or slightly less. Intravenous nitroglycerin was then restarted and the dosage titrated upward to achieve the previously described effect on the wedge pressure. Nominal variables (sex, edema) were compared using Fisher's exact test. All other comparisons between responders and nonresponders were established using the 2-tailed, 2-sampled* t *test. All values were expressed as mean ± 1 standard deviation. A p value <0.05 was considered statistically significant.*

*Sixteen patients (responders) achieved the desired hemodynamic end point after intravenous nitroglycerin (average dose 85 ± 7 μg/min); wedge pressure was 23 ± 4 mm Hg before treatment and decreased to 13 ± 3 mm Hg after treatment. In 12 patients wedge pressure was restored to a normal range (10 to 14 mm Hg) and in 4 reduced to ≥30% of the baseline value. Mean right atrial pressure was 10 ± 3 mm Hg before treatment and 5 ± 3 mm Hg after treatment (Figure 1).*

*Ten patients (nonresponders) were unable to achieve the desired end point after initial treatment with intravenous nitroglycerin (dosage range 150 to 400 μg/min). Right atrial and wedge pressures were 17 ± 4 and 29 ± 6 mm Hg before treatment and 16 ± 4 and 27 ± 5 mm Hg after treatment, respectively (Figure 1).*

*Intravenous furosemide (40 mg) was given every 6 hours over 0.5 to 3 days to these 10 nonresponding patients until a right atrial pressure of approximately ≤10 mm Hg was reached. After diuresis right atrial pressure was 9 ± 2 mm Hg and wedge pressure was 22 ± 4 mm Hg. After readministration of intravenous nitroglycerin (mean 164 ± 135 μg/min), right atrial and wedge pressures decreased to 6 ± 3 and 13 ± 2 mm Hg, respectively.*

**TABLE I** Clinical and Hemodynamic Profile of Responcers and Nonresponders to Intravenous Nitroglycerin

| | Responders | Nonresponders | p Value |
|---|---|---|---|
| No. of patients | 16 | 10 | |
| Age (years) | 74 ± 13 | 66 ± 12 | NS |
| Men | 11 | 3 | NS |
| Women | 5 | 2 | |
| Peripheral edema | 2 | 7 | p <0.05 |
| Ejection fraction (%) | 33 ± 14 | 33 ± 17 | NS |
| Hemodynamic variables | | | |
| Right atrial pressure (mm Hg) | 10 ± 3 | 17 ± 4 | p <0.05 |
| Wedge pressure (mm Hg) | 23 ± 4 | 29 ± 6 | NS |
| Cardiac index (liters/min/$m^2$) | 2.0 ± 0.6 | 2.0 ± 0.3 | NS |
| Stroke volume index (ml/$m^2$) | 21 ± 8 | 23 ± 8 | NS |
| Systemic vascular resistance index (dynes · s · $cm^{-5}$ · m) | 3,308 ± 1,175 | 2,810 ± 1,130 | |

NS = not significant.

Intravenous nitroglycerin is frequently used for treating CHF. Decreased venous return and ventricular filling pressures, a principal physiologic effect of nitroglycerin, derives from its vasodilatory action on the venous capacitance vessels.[9,10]

Several reports in the last decade have underscored the wide spectrum of responses to intravenous nitroglycerin and other nitrate preparations in CHF.[3,6,7,11,12] Many explanations have been offered for nitrate resistance: peripheral edema with decreased venous compliance, a maximally dilated and engorged venous system due to an elevated right atrial pressure, excessive venoconstriction due to augmented catecholamines, limited bioavailability of the drug, and failure at the cellular level.[5,7,11]

Hemodynamic resistance to nitrates is usually inferred when wedge pressure reduction is <20 to 30% of the baseline value. In a study by Armstrong et al,[11] intravenous nitroglycerin failed to achieve a wedge pressure reduction of ≥25% in 31% of patients with CHF despite doses exceeding 400 μg/min. Those patients with primary resistance to nitroglycerin had a substantially

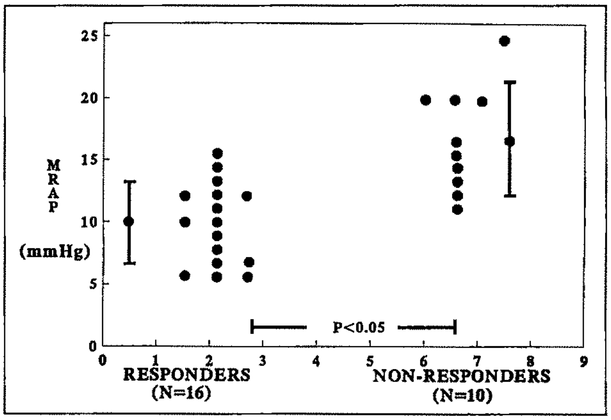

**FIGURE 1. Individual and group values of mean right atrial pressure (MRAP) for 26 patients (16 responders and 10 nonresponders) who received intravenous nitroglycerin.**

higher right atrial pressure than those who did respond (19 ± 4 vs 10 ± 4 mm Hg). A higher incidence of hemodynamic resistance to oral isosorbide dinitrate in severe CHF was found by Kulick et al.[12] Whereas all patients with initial right atrial pressures of <7 mm Hg responded to a dose of 40 mg with a significant decrease wedge pressure, only half of the patients with a right atrial pressure >7 mm Hg responded to a similar nitrate dose; and 25% of patients were unable to respond to an even higher dose of 80 to 120 mg.

In another study by Magrini and Niarchos,[7] approximately 50% of patients with CHF who had no hemodynamic effect to sublingual nitroglycerin (1.6 to 2.4 mg) were identified as having massive peripheral edema. This high incidence of ineffective hemodynamic response to nitroglycerin was attributed to impaired venodilatation incident to subcutaneous fluid accumulation and increased mechanical compression.

In our study, 10 of 26 patients (39%) who received intravenous nitroglycerin for CHF, did not respond with a reduction in wedge pressure (<30% of baseline) despite high infusion rates of 400 μg/min. Nonresponders to intravenous nitroglycerin had a higher incidence of clinical peripheral edema ($p < 0.05$) and a significantly higher baseline right atrial pressure than those who did respond (17 ± 4 vs 10 ± 3 mm Hg, $p < 0.05$) (Table I). Whereas only 7 of 17 patients (41%) had an effective hemodynamic response when the pretreatment right atrial pressure was >10 mm Hg, all patients with a right atrial pressure of ≤10 mm Hg successfully responded to intravenous nitroglycerin. A restored hemodynamic response to intravenous nitroglycerin was then observed (wedge pressure 22 ± 4 to 13 ± 2 mm Hg) in the 10 patients with primary nitrate resistance after vigorous diuretic therapy cleared peripheral edema and reduced right atrial pressure to ≤10 mm Hg.

The restoration of venous responsiveness to intravenous nitroglycerin after prompt reduction in right atrial pressure (≤10 mm Hg) concurs with the findings of previous reports and lends credence to the predominant role of an elevated right atrial pressure with or without concomitant peripheral edema as the principal underlying cause of hemodynamic resistance to intravenous nitroglycerin infusion. In the setting of a high systemic venous pressure, moreover, the presence of tissue edema may further mechanically compress peripheral veins and severely compromise the action of nitrates on venodilatation.

Hemodynamic monitoring (Swan-Ganz catheter) may be recommended when intravenous nitroglycerin is initiated for the therapy of severe CHF, especially for patients deemed difficult to treat. These measurements will not only guide titration and dosage of intravenous nitroglycerin, but also identify those patients who are unable to achieve an optimal wedge pressure and remain hemodynamically refractory. In the setting of primary nitroglycerin failure, hemodynamic responsiveness to this drug may be restored after the use of diuretics that enable reduction of right atrial pressure to ≤10 mm Hg.

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# A Symposium: Ventricular Remodeling and Unloading Following Myocardial Infarction

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# Ventricular Enlargement and Remodeling Following Acute Myocardial Infarction: Mechanisms and Management

Eugene Braunwald, MD, and Marc A. Pfeffer, MD, PhD

**Severe myocardial ischemia, when sustained, leads to a predictable sequence of events, including myocardial necrosis, expansion of the infarct, and later its replacement by scar tissue. The nonischemic tissue sustains ventricular function, but it frequently adapts to the extra load placed on it by dilating. The enlargement and remodeling of the left ventricle may lead to ventricular failure and arrhythmias. Rational management to prevent these complications includes restoration of the patency of the occluded vessel and ventricular unloading. These two interventions may be useful both early and late in the course of infarction.**

**(Am J Cardiol 1991;68:1D–6D)**

There is considerable variability in the natural history of acute myocardial infarction (AMI). Although the majority of patients recover uneventfully, complications still occur in a substantial number. These complications, which are often associated with reduced long-term survival, may be divided into 3 major groups: (1) pump failure, which early in the course may lead to cardiogenic shock and pulmonary edema, and later to chronic congestive heart failure; (2) electrical instability, which may cause ventricular tachyarrhythmias and sudden unexpected death; and (3) recurrent ischemia and infarction. Prevention of these complications requires an understanding of the pathophysiologic consequences of coronary artery occlusion. This article, indeed this supplement, deals primarily with the first group of these complications, pump failure, and its prevention.

## EFFECTS OF CORONARY OCCLUSION

It has been appreciated for more than a century that following acute coronary occlusion a number of drastic changes occur in the structure and function of the myocardium previously perfused by the obstructed vessel.[1] More recently, it has become clear that important changes also take place in the remainder of the myocardium. The consequent alterations in the topography of the left ventricle (ventricular remodeling) represent an important consequence of myocardial infarction.[2]

With the sudden onset of severe myocardial ischemia, caused by a reduction of blood flow to less than approximately 20% of normal (Figure 1 [1]), the contractile function of the heart rapidly becomes impaired. As was pointed out by Tennant and Wiggers in 1935,[3] within seconds of coronary occlusion the severely ischemic myocardium ceases to contract. For a relatively brief period, approximately 15–20 minutes in the anesthetized dog and a similar but more variable period in conscious humans, the ischemic myocardium is reversibly damaged (Figure 1 [2]). Restoration of perfusion

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during this period results in a return to normal myocardial function, albeit after what may be a prolonged period of postischemic left ventricular dysfunction (myocardial stunning).[4] The duration of the period in which the ischemic myocardium remains reversibly injured is a function of the balance between its residual oxygen supply and demand. Thus, incomplete or "stuttering" coronary occlusion and/or the presence of a rich network of collaterals prolongs the period of reversible injury, whereas tachycardia and a heightened sympathetic state increase myocardial oxygen demands and abbreviate this period.

At the termination of the period of severe, reversible ischemic injury, myocyte necrosis commences, and if severe ischemia persists, myocardial infarction is completed in approximately 3–6 hours (Figure 1 [3]). The duration of this critical period also appears to depend on the relation between oxygen supply and demand. In the anesthetized dog, a "wavefront" of necrosis proceeds from the subendocardium to the subepicardium,[5] and this is often the case in the human as well. When myocardial ischemia and/or infarction is transmural, the injured tissue bulges paradoxically when ventricular pressure rises during systole, i.e., it exhibits dyskinesis.

In the case of many infarcts, especially large, anterior ones, infarct expansion occurs during the hours and days following infarction (Figure 1 [4]); the necrotic myocardium thins and elongates. It is "pulled apart" as necrotic myocytes slide along one another.[6,7] There is a reduction in the number of myocytes across the infarcted wall,[8] and the volume of the left ventricular cavity is increased. A high intraventricular systolic pressure,[9] lack of preexisting hypertrophy of the ventricular wall, and a large transmural anterior infarction all increase the likelihood of infarct expansion,[10] aneurysm formation,[10] and cardiac rupture.[11,12] The latter complication, still an important cause of death in AMI,[13] may be considered to be an extreme form of infarct expansion.[7]

A number of processes make the infarcted tissue less distensible and thereby reduce or even abolish the dyskinesis; these include the early development of edema and of an inflammatory infiltrate in the necrotic myocardium. Healing of the infarct occurs by fibroblast proliferation, collagen deposition, and ultimately by replacement of varying portions of the infarct by scar tissue[14,15] (Figure 1 [5]), which commences several days after infarction and may not be complete for many months (Figure 1 [6]). A firm scar is obviously less distensible than soft, fresh necrotic myocardium, but recent evidence suggests that it too may elongate as a consequence of distending forces.[16] Corticosteroids and nonsteroidal antiinflammatory agents (NSAIDs) that reduce edema and inflammation provoke infarct thinning and increase the likelihood of aneurysm formation and myocardial rupture.[17,18]

The nonischemic myocardium is also affected by the development of severe ischemia and then infarction.[19] Acute occlusion of a major coronary artery and the resultant dyskinesis of a large portion of the ventricular wall, as well as the pain and fright that often accompany large infarcts, activate the adrenergic–adrenal medullary system with resultant stimulation of β-adrenoreceptors and increased contractility of the nonischemic myocardium. This acts to sustain global ventricular function in the presence of dyskinesis of the ischemic or infarcted myocardium. If the artery

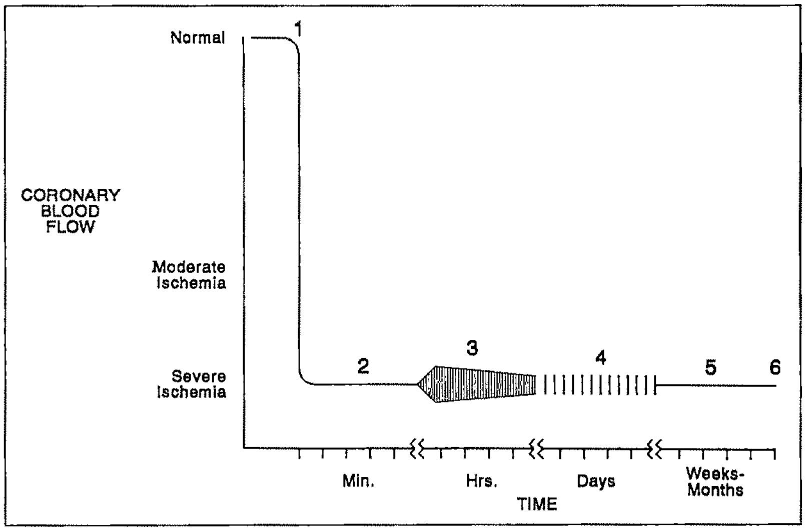


**FIGURE 1. Temporal sequence of events following sudden reduction of coronary blood flow (1). During the following minutes, the severely ischemic myocardium is reversibly ischemic (2). This is followed by a period of several hours during which progressive necrosis occurs (3). Infarct expansion takes place over the next several days (4), followed by scar formation and replacement of a portion of the ventricle by scar tissue (5). Healing is complete several months after the beginning of the process (6).**

perfusing the nonischemic tissue is not obstructed, coronary blood flow may increase transiently to satisfy the augmented myocardial oxygen demands (Figure 2 [7]) and then it returns to control levels (Figure 2 [8]). With the waning of the adrenergic–adrenal medullary stimuli, the contraction of the nonischemic myocardium is enhanced instead through the operation of the Frank–Starling mechanism. Akinesis and dyskinesis of the damaged myocardium impair ventricular emptying, which increases the preload acting on the viable, nonischemic heart muscle. As a consequence, the ventricle dilates[20] and becomes more spherical. With cardiac dilation, myocardial wall tension increases, according to Laplace's law (which relates wall tension to the product of intraventricular pressure and radius divided by wall thickness). This increase in wall tension may cause further dilation of the non-necrotic tissue[21] and a vicious cycle in which dilation "begets" further dilation, which may lead to left ventricular failure.[22] On the other hand, if the patient survives and develops hypertrophy of the nonischemic myocardium,[21] myocardial wall tension tends to be restored toward (but perhaps not all the way to) normal.[23]

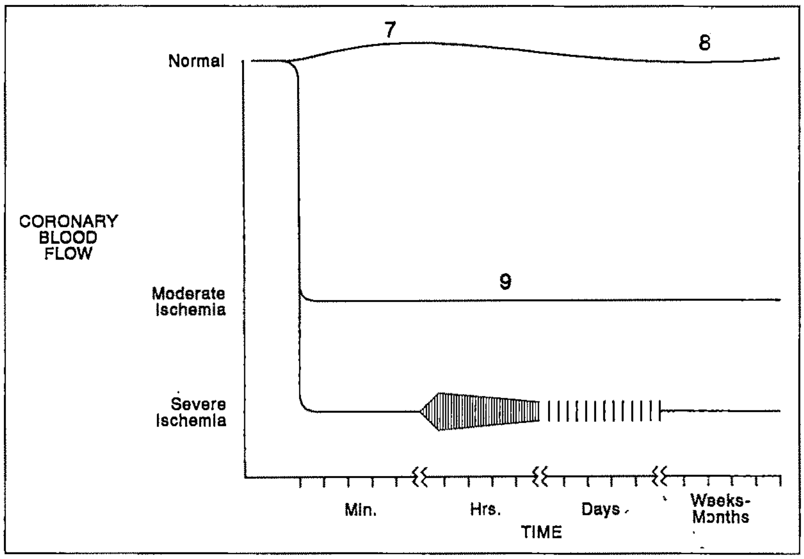
The events in the noninfarcted myocardium outlined above can be affected importantly by the degree of patency of the noninfarct-related coronary arteries. When one or more of these vessels is severely obstructed, the oxygen supply may not be adequate to meet the augmented oxygen demands of the noninfarcted tissue. This process may, in turn, increase the quantity of myocardium that is ischemic, interfere further with ventricular function, and/or lead to recurrent infarction. In myocardium that is rendered chronically ischemic by a subtotal coronary obstruction (Figure 2 [9]) the contractile activity is reduced, sometimes to the point of akinesis, but viability may persist; this condition has been referred to as "myocardial hibernation."[24,25]

## SEVEN PRINCIPLES IN THE MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION TO PRESERVE FUNCTION AND TOPOGRAPHY

**Prevention of infarction of severely ischemic myocardium:** The foregoing considerations suggest 7 principles that may be useful in the management of AMI. The first is the prevention of infarction. Immediately following thrombotic occlusion of an atheromatous coronary artery, powerful prothrombotic and antithrombotic forces oppose one another. Most often the antithrombotic forces are dominant and for this reason many coronary occlusions are incomplete and/or transient. Such incomplete or transient occlusions may be manifested clinically as repetitive episodes of unstable angina, with evidence of transient ischemia at rest (ischemic pain, electrocardiographic changes, and impaired contraction), but without evidence of myocardial infarction. Patients with unstable angina are at much higher risk of acute myocardial infarction than are patients with chronic stable angina, and the administration of aspirin and/or heparin reduces the incidence of myocardial infarction,[26] probably by tilting the balance in favor of the antithrombotic forces and thereby restoring normal coronary blood flow (Figure 3 [A]).

**Early reperfusion to limit myocardial infarction:** If spontaneous or drug-induced thrombolysis occurs before infarction is complete, a nontransmural infarct develops. When coronary arteriography is carried out during the first 4 hours following the onset of symptoms, about 15% of vessels are

**FIGURE 2. Events in the myocardium other than that perfused by the infarct-related coronary artery. Contractility of the nonischemic myocardium is stimulated by adrenergic-adrenal medullary influences, transiently augmenting the oxygen needs of and coronary blood flow to the nonischemic myocardium (7). Later, blood flow to the nonischemic myocardium returns to baseline (8). When the initial events that precipitated ischemia cause subtotal coronary obstruction, the myocardium becomes moderately ischemic (9); it may remain viable but lose its contractile properties, i.e., be converted to "hibernating" myocardium.**



already patent, probably reflecting spontaneous thrombolysis.[27] The percentage of occluded vessels that regain patency increases progressively with time.[27,28] Thrombolytic therapy or early mechanical revascularization may be viewed, like heparin and aspirin in the case of unstable angina, as a means of tilting the balance of forces against the thrombus (Figure 3 [E]). Early reperfusion may salvage a rim of epicardium, prevent the development of a transmural infarct, and thereby minimize infarct expansion and its consequences. Sometimes, particularly with thrombolytic therapy, myocardial blood flow is raised sufficiently to halt infarct progression but not sufficiently to restore normal contractility of the jeopardized myocardium (Figure 3 [B$^1$]). When a thrombus is lysed, powerful prothrombotic forces are unleashed that can cause prompt coronary reocclusion Therefore, it is desirable to treat patients who receive thrombolytic agents with anticoagulants and/or agents that interfere with platelet aggregation. There is considerable evidence that the earlier that reperfusion occurs, the more jeopardized myocardium can be salvaged, the less the impairment of left ventricular function,[29] and the lower the mortality.[30] Thus, early restoration of coronary arterial patency and persistence of patency are important therapeutic goals.

**Load reduction to limit myocardial infarction:** An important therapeutic goal in patients with infarcting myocardium is to diminish the load acting on the left ventricle and its oxygen requirements, thereby salvaging jeopardized cardiac muscle. Reducing myocardial load during the first few minutes of ischemia may diminish ischemia and thereby prevent infarction (Figure 3 [D$_2$]), or diminish infarct size (Figure 3[D$_3$]). Reduction of wall tension by nitroglycerin during the period of reversible ischemia or early in the course of infarction appears to be beneficial.[31–33] The administration of angiotensin-converting enzyme inhibitors early during this period may also be useful in reducing infarct dilation.[34]

**Prevention or limitation of reperfusion injury:** Although early reperfusion may successfully salvage reversibly damaged ischemic cardiac muscle, it may simultaneously accelerate necrosis of other reversibly injured tissue, at least in part as a consequence of the release of oxygen-derived free radicals.[35,36] Accordingly, reperfusion of severely ischemic and infarcting myocardium has been referred to as a "double-edged sword."[37] A fourth principle of management of the patient with AMI consists of the prevention of reperfusion *injury* by substances such as free radical scavengers (which may include sulfhydryl-containing angiotensin-converting enzyme inhibitors).[38] Although some studies in experimental animals support this therapeutic approach,[39] the results have not been uniform and this approach has not yet been validated clinically.

**Ventricular unloading after completion of the infarct:** Once the infarct is completed, attention should focus on prevention of infarct expansion and on dilation of the viable myocardium (Figure 3

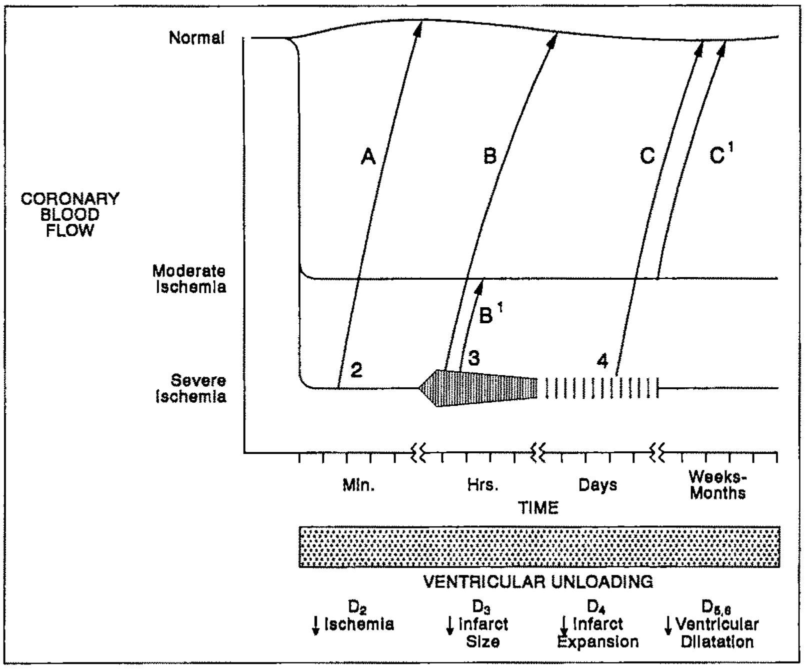


**FIGURE 3. Therapeutic maneuvers in various stages of ischemia and infarction. Severely ischemic tissue (2) may be reperfused, thereby averting myocardial infarction (A). Infarcting tissue (3) may be reperfused leading to sparing of myocardial tissue (B). If blood flow is restored only in part (B$^1$) the myocardium may remain noncontractile, although viable, i.e., hibernating. After completion of the infarct (4) late reperfusion (C) may still be useful, as described in the text. Mechanical reperfusion of moderately ischemic myocardium (C$^1$) may restore contractility of hibernating myocardium to normal. Ventricular unloading may be useful throughout the preinfarct and postinfarct periods. Unloading may reduce ischemia, (D$_2$), infarct size (D$_3$), infarct expansion (D$_4$) and ventricular dilation (D$_{5,6}$).**

[$D_{4,5,6}$]). The chronic administration of orally active angiotensin-converting enzyme inhibitors have been shown to be effective in the development of cardiac dilation in humans[40] and to prolong survival in rats with myocardial infarction.[41] These agents may also exhibit an antiischemic effect,[42,43] perhaps by inhibiting the formation of angiotensin II in the walls of the coronary arteries,[44,45] reduce the ischemia of the remaining jeopardized tissue, and in this manner perhaps reduce the incidence of reinfarction, an important predictor of late mortality in postinfarct patients.

**Establishing late patency of the infarct-related artery:** There is increasing evidence, albeit suggestive, that restoration of patency of an occluded coronary artery may be useful even after the infarct has been completed[46] (Figure 3 [C]). An open artery may provide a scaffold that limits the distensibility of the infarct and, therefore, the extent of dyskinesis. An open infarct-related artery may also prevent ventricular dilation[47,48] reduce electrical instability[49] and provide perfusion of other jeopardized areas of myocardium through collaterals. Late reperfusion, i.e., after infarct completion, may occur spontaneously, with the aid of thrombolytic agents or as a result of mechanical intervention. Revascularization of viable, but noncontracting (hibernating) myocardium (Figure 3 [$C^1$]) is usually followed by restoration of normal contractile activity,[24,25] which in turn may reduce the load on the remaining normal myocardium and thereby limit its dilation.

**Prevention of scar thinning:** Corticosteroids and nonsteroidal antiinflammatory agents (indomethacin, ibuprofen) may interfere with infarct healing and the thin scar may aggravate the dyskinesis, cause formation of a ventricular aneurysm or, rarely, myocardial rupture.[17,18,50] Fortunately, aspirin does not appear to exert this deleterious effect[50] and for this reason it is the agent of choice in patients in the early stages after myocardial infarction who require antiinflammatory agents for complications such as acute pericarditis or Dressler's syndrome.

## DISCUSSION

Remodeling of the ventricle following acute myocardial infarction results from the loss of contractile function of the necrotic tissue, from expansion of the infarct and from compensatory dilation of the nonischemic myocardium. An understanding of these pathophysiologic processes can lead to rational therapy that may involve restoration of patency of the infarct-related artery and reduction of the load placed on the ventricle. These 2 approaches may be useful both early and late in the course of the infarction.

This supplement to the *American Journal of Cardiology* provides the proceedings of a symposium entitled: "Post Infarction: Ventricular Unloading and Remodeling," at which these concepts were discussed in detail. Several clinical trials are now ongoing that are designed to test whether these concepts can be applied to improve the outcome in patients after myocardial infarction. Four of these trials are described in detail herein.

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# Cellular Basis of Ventricular Remodeling After Myocardial Infarction

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**To determine whether acute left ventricular failure associated with myocardial infarction leads to architectural changes in the spared nonischemic portion of the ventricular wall, large infarcts were produced in rats, and the animals were sacrificed 2 days after surgery. Left ventricular end-diastolic pressure was increased, whereas left ventricular *dP/dt* and systolic pressure were decreased, indicating the presence of severe ventricular dysfunction. Absolute infarct size, determined by measuring the fraction of myocyte nuclei lost from the left ventricular free wall, averaged 63%. Transverse midchamber diameter increased by 20%, and wall thickness diminished by 33%. The number of mural myocytes in this spared region of the left ventricular free wall decreased by 36% and the capillary profiles by 40%. Thus, side-to-side slippage of myocytes in the myocardium occurs acutely in association with ventricular dilation after a large myocardial infarction. In order to analyze the chronic consequences of myocardial infarction on ventricular remodeling, a second group of experiments was performed in which the left coronary artery was ligated and the functional and structural properties of the heart were examined 1 month later. In infarcts affecting an average 38% of the free wall of the left ventricle (small infarcts), reactive hypertrophy in the spared myocardium resulted in a complete reconstitution of functioning tissue. However, left ventricular end-diastolic pressure was increased, left ventricular *dP/dt* was decreased, and diastolic wall stress was increased 2.4-fold. After infarctions resulting in a 60% loss of mass (large infarcts), a 10% deficit was present in the recovery of viable myocardium. Functionally, ventricular performance was markedly depressed, and diastolic wall stress was increased 9-fold. The alterations in loading of the spared myocardium were due to an increase in chamber volume and a decrease in the myocardial mass/chamber volume ratio that affected both infarct groups. Thus, decompensated eccentric ventricular hypertrophy develops chronically after infarction and growth processes in myocytes are inadequate for normalization of wall stress when myocyte loss involves nearly 40% or more of the cells of the left ventricular free wall. The persistence of elevated myocardial and cellular loads may sustain the progression of the disease state toward end-stage congestive heart failure.**

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Human[1–4] and animal[4–7] studies of the effects of myocardial infarction on ventricular architecture have demonstrated that the injured ventricle progressively enlarges with time and that this alteration is paralleled by a corresponding decline in cardiac performance.[2,8,9] Moreover chamber dilation is not accompanied by a proportional increase in wall thickness[1–9] so that the ratio of wall thickness to chamber radius is not maintained and decompensated ventricular hypertrophy occurs.[10] The gross morphologic indices of ventricular dimensions, that is, wall thickness and chamber radius, are the expression of a combination of parameters, including the number of myocytes across the wall, the average myocyte cross-sectional diameter and length, and the volume composition of the myocardium. For example, chamber dilation and wall thinning may come about from side-to-side slippage of myocytes within the wall,[11–13] which will result in a reduction in the number of mural cells. Were this phenomenon to occur, however, the proportion between the myocyte compartment and the other constituents of the tissue, including the vascular framework, would remain constant. On the other hand, myocyte hypertrophy by cell lengthening alone could be expected to result in a large cavity volume without altering wall thickness, whereas increases in the

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lateral dimension of myocytes would have the effect of increasing wall thickness with no change or a decrease in chamber volume.[10,14–17] Thus, ventricular remodeling after a segmental loss of functioning tissue may involve acute movements of cells in the wall and chronic responses dictated by the characteristics of the reactive hypertrophic adaptation of the remaining viable myocytes. Although growth of the unaffected ventricular mass is an early event,[15] it continues to occur throughout the healing process[18] and long thereafter,[6,17] leading to a progressive increase in size of the spared myocytes so that most of the originally lost myocardium is replaced by fewer enlarged ventricular cells.[17,19] Since it is current view that myocyte growth in hypertrophy is proportional to the amount of stress imposed on the heart,[14] the definition of the structural and functional properties of the infarcted ventricle becomes important in the recognition of how the remodeling of the wall interacts with cardiac hemodynamic parameters in the characterization of the loading state of the myocardium after ischemic necrosis. The Laplace load on the viable cells will be highly dependent on the anatomic rearrangements that govern the relation between wall thickness, number of cells across the wall, chamber radius, and resultant myocardial function.[1,2,9,10]

## MYOCARDIAL INFARCTION AND ACUTE VENTRICULAR REMODELING

After acute myocardial infarction, pump function is reduced in direct proportion to the extent of myocardium that is lost on an obligatory basis, i.e., ejection fraction falls as a function of infarct size.[21–23] Infarcts affecting 45% or more of the left ventricle generate severe myocardial dysfunction that may result in sudden cardiac death or acute congestive heart failure.[24,25] Patients who survive the acute phase may have a significant deterioration of left ventricular function when the loss of contractile mass may be too great to be compensated for by the residual myocardium, although some improvement occurs in weeks and months following the initial event.[26–28] Two critical questions remain to be answered for the understanding of the capacity of the heart to sustain large destruction in muscle mass: the first concerns the magnitude and nature of the alterations in the loading state of the myocardium,[15–17] and the second concerns the effectiveness of the unaffected myocytes to reconstitute functioning tissue.[29] Therefore, the early reaction of the left and right ventricles after an acute segmental loss of myocardium was analyzed morphometrically to determine the tissue, cellular, and vascular adaptations involved in the overall remodeling of the wall after infarction.[30] The significance of evaluating these quantitative properties of the surviving myocardium lies in the estimation of whether this spared tissue can undertake immediate regenerative processes that would tend to compensate for the loss of muscle mass and function or whether the growth capacity of this tissue is impaired by the severe stress, so that the initial recovery of the ventricle is in greater jeopardy.

**Ventricular anatomy and wall stress acutely after infarction:** Two days after occlusion of the left coronary artery near its origin in rats, a severe impairment of global ventricular function was documented by a 19% decrease in mean arterial blood pressure, a 17% reduction in left ventricular systolic pressure, and a 5-fold increase in left ventricular end-diastolic pressure. Moreover, a substantial decrease in $+dP/dt$, $-30\%$, was evident in infarcted hearts, further indicating the occurrence of left ventricular failure following coronary artery ligation.[30] The changes in chamber diameter and in the thickness of the spared portion of the left ventricular wall bordering the infarcted myocardium, i.e., border zone, and the unaffected interventricular septum, i.e., remote healthy myocardium, are illustrated in Figure 1. The event of myocardial infarction was associated with a 20% increase in midchamber luminal diameter and a 33% thinning of the wall bordering the necrotic zone, whereas septal thickness decreased by 23%.

To establish whether these dimensional changes of the infarcted ventricle in combination with the impairment of cardiac hemodynamics resulted in an alteration in tension on the surviving myocardium, diastolic wall and septal stresses were computed from the Laplace relation. In comparison with sham-operated rats, diastolic wall and septal stresses increased by 8-fold and 7-fold, respectively (Figure 2). By assuming that systolic contraction affects fiber length by 15% in control animals, systolic wall and septal stresses were calculated from diastolic measurements and were 1,013 and 1,128 dynes/mm$^2$, respectively. Even under a very unlikely condition of little or no shortening in the diseased ventricle, corresponding systolic stress values would be 1,129 and 1,237 dynes/mm$^2$, respectively. These changes would imply increases of 11% and 10% in the free wall and septum, which were significantly smaller than those found in diastolic stress.

To evaluate the relation between these functional–anatomic changes and infarct size, absolute infarct size was determined by measuring the percent loss of myocyte nuclei in the infarcted ventricle. Because the number of nuclei in ventricular myocytes does not change in adult rats after myocardial infarction,[31,32] the fraction of nuclei lost from the whole ventricle is identical to the fraction of tissue destined to become necrotic after coronary artery ligation.[15,17,19] Coronary occlusion produced a 63% loss of myocyte nuclei in the left ventricular free wall, whereas the number of nuclei in the septum was not affected by the surgical procedure (Figure 3). If the septum and free wall were combined, a 43% reduction in the total number of ventricular nuclei was found.

In summary, large infarcts of the left ventricle lead to acute ventricular dilation and wall thinning, which in combination with the alterations in cardiac hemodynamics result in a marked elevation in diastolic stress of the spared portion of the free wall and interventricular septum. Thus, global myocardial remodeling after infarction generates a condition of overload on the surviving myocardium that consists primarily of a volume component, although a pressure element is operative as well. This functional state can be expected to induce a hypertrophic response of the unaffected cells, characterized by an increase in myocyte length that should exceed the lateral expansion of the cells.[10,14,33] A pattern of growth consistent with this analysis has been found in animal[15–17] and human[1,9] studies of myocardial infarction early and late after the initial ischemic event.

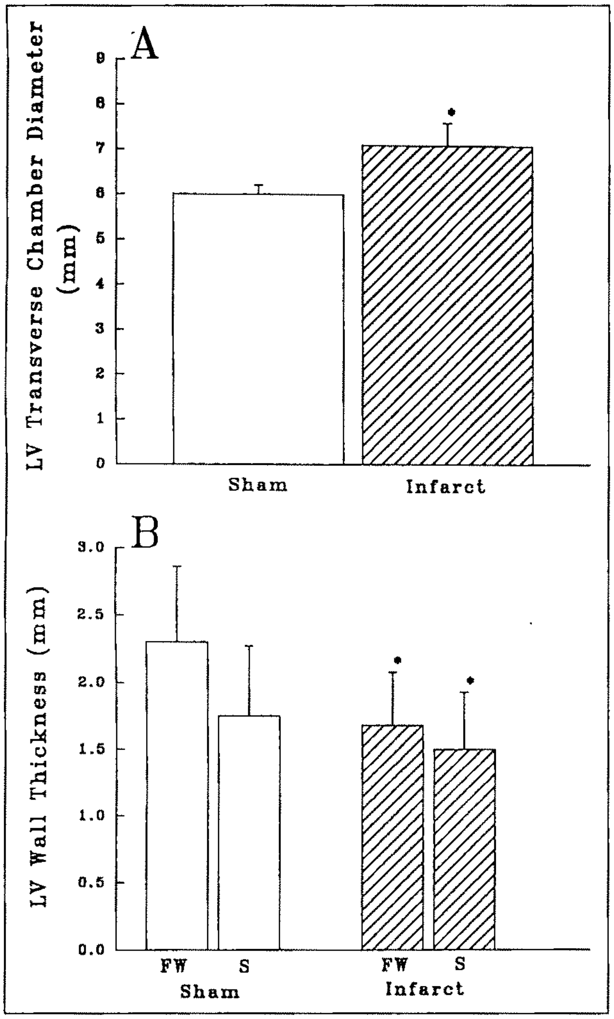

**FIGURE 1. Changes in left ventricular (LV) chamber diameter and in the thickness of the spared portion of the left ventricular free wall (FW) and interventricular septum (S) 2 days after acute myocardial infarction. Values are mean ± standard deviation. *p <0.05.**

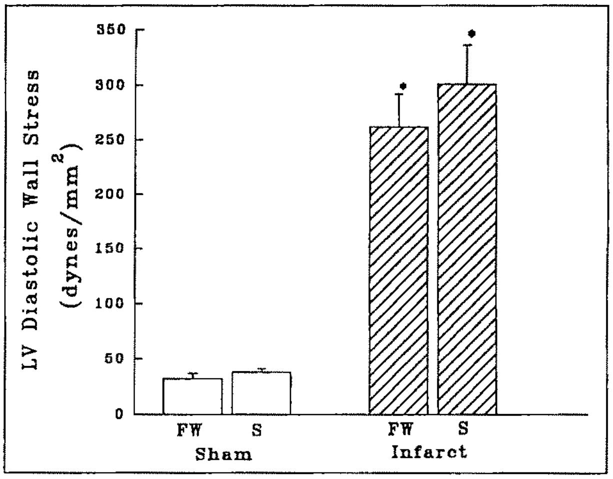

**FIGURE 2. Changes in diastolic stress in the spared portion of the left ventricular (LV) free wall (FW) and interventricular septum (S) 2 days after acute myocardial infarction. Values are mean ± standard deviation. *p <0.05.**

**Cell movement and wall and chamber remodeling acutely after infarction:** As stated before, the identification of the structural mechanisms

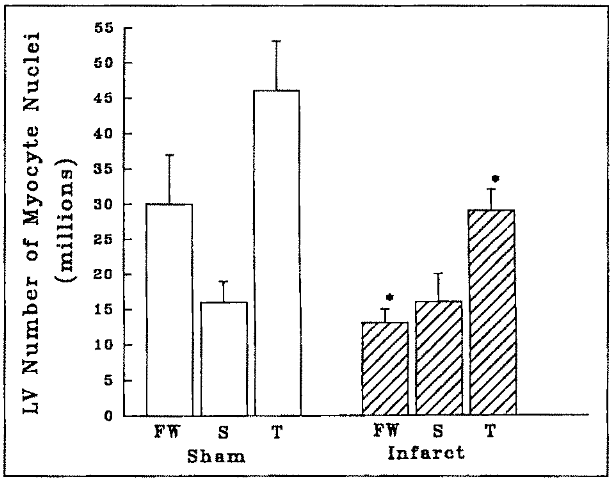

**FIGURE 3. Changes in the total number of myocyte nuclei in the left ventricular (LV) free wall (FW), interventricular septum (S), and entire left ventricle inclusive of the septum (T) 2 days after acute myocardial infarction. Values are mean ± standard deviation. *p <0.05.**

implicated in the adaptation of the ventricular wall following myocardial infarction requires the knowledge of the changes in size and shape of myocytes, which are shown together in Figure 4. Two days after coronary artery occlusion, myocyte cell volume in the surviving portion of the free wall and septum increased 22% and 16%, respectively. These cellular enlargements were due to 8% and 5% increases in cross-sectional area and 13% and 11% augmentations in average myocyte length. The increases in the lateral and longitudinal dimensions were not statistically significant, but the combination of these effects produced statistically significant increases in myocyte cell volume in both the border zone and remote myocardium.

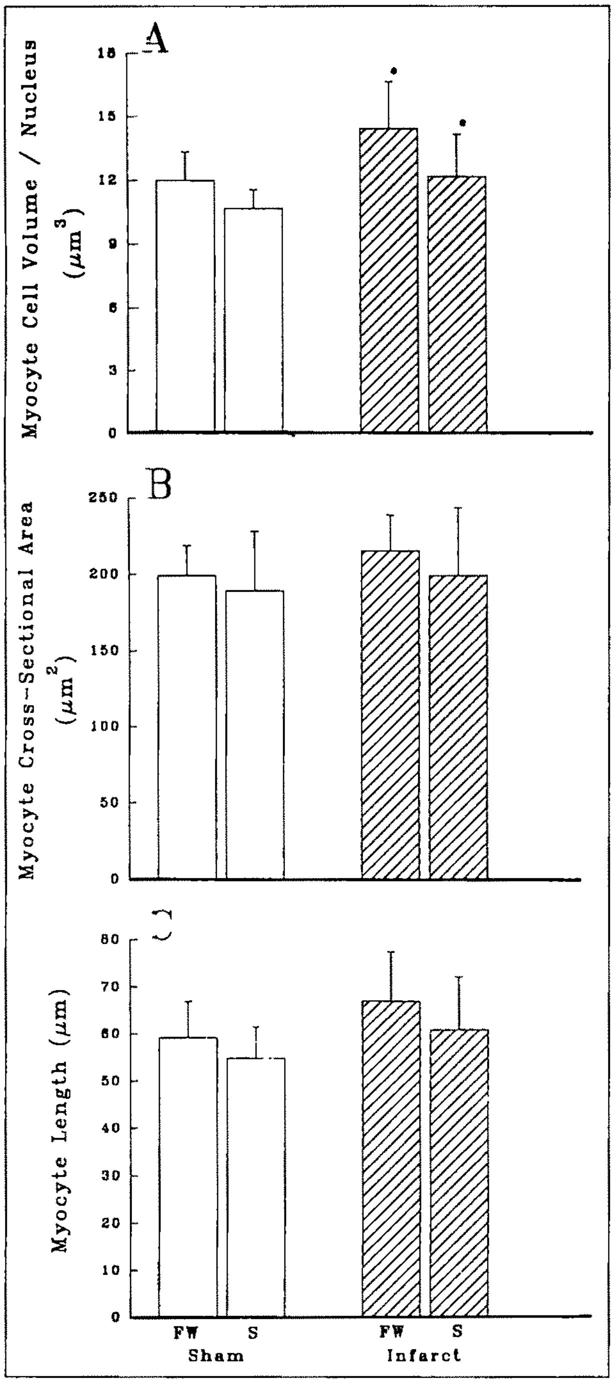

**FIGURE 4. Changes in the dimensional properties of the spared myocytes in the left ventricular free wall (FW) and interventricular septum (S) 2 days after acute myocardial infarction. Values are mean ± standard deviation. *p <0.05.**

The increase in myocyte diameter with infarction appears to be in contrast to the decrease in ventricular wall thickness illustrated in Figure 1. However, when the number of myocytes across the region of the wall bordering the necrotic tissue and the remote myocardium was measured, a 36% and a 24% reduction in this quantity was found (Figure 5). As demonstrated in the lower panel of Figure 5, the structural reorganization of myocytes was accompanied by a comparable phenomenon in the capillary network because the number of transmural capillaries decreased by 40% and 26% in the ventricle and septum, respectively. The close correspondence of the changes in wall thickness, 33% in

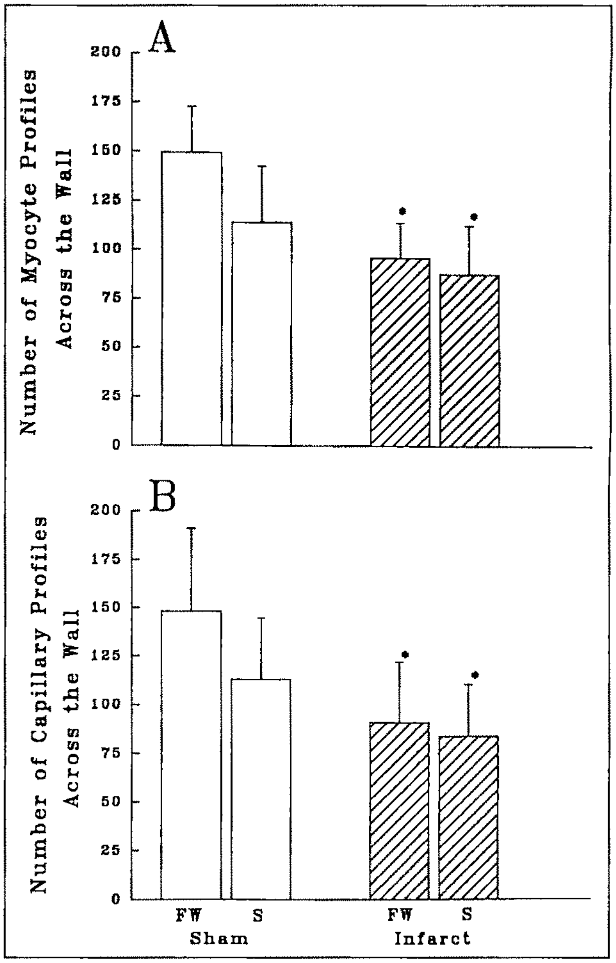

**FIGURE 5. Changes in the number of myocyte and capillary profiles across the left ventricular free wall (FW) and interventricular septum (S) 2 days after acute myocardial infarction. Values are mean ± standard deviation. *p <0.05.**

the border zone and 23% in the remote myocardium, with those in the number of mural myocytes and capillaries in the free wall and septum, was due to the fact that the increases in cross-sectional diameter of myocytes were essentially negligible, being 4% in the wall and 2.5% in the septum.

Muscle fiber slippage after myocardial infarction has been suggested to occur in both animals and humans[4,34] and has been assumed to be the only mechanism implicated in the thinning of the wall acutely after irreversible ischemic injury. Methodologic limitations, however, have left these conclusions tentative. The results already discussed[30] have characterized not only the occurrence of this phenomenon in quantitative terms but also the difference in its distribution and magnitude between the surviving myocardium bordering and that remote from the infarct. Moreover, the contribution of the capillary network to wall remodeling was unexpected and without precedent. Thus, lateral slippage of myocytes is an early event that may condition the onset, development, and progression of the dilated cardiomyopathy that may evolve after an acute myocardial infarction.

As a result of side-to-side slippage, the rings of cells that have moved radially toward the epicardial region have to enlarge to adapt to the new circumference associated with a greater chamber diameter.[35] Moreover, the sliding of myocytes from the endocardial to the epicardial surface of the ventricular wall must result in an increase in the longitudinal axis of the heart proportional to the extent of cell slippage. Thus, the reduction of cells in the transverse direction leads to an increase in the number of cells in the longitudinal axis. The major axis of the ventricle will then increase by a factor that contains 3 variables: number of cells, average cell diameter, and the angle of orientation of muscle cells with respect to the longitudinal diameter of the heart. Physical alterations in the connective tissue compartment involving either breakage of the collagen structures interconnecting myocytes or distortion of the struts laterally tethering muscle cells[36] have to take place to allow this process to occur.

The recognition that side-to-side slippage of myocytes within the wall affects not only transverse chamber diameter, but also the longitudinal axis of the ventricle has important implications for sudden increases in chamber volume and in the loading state of the myocardium. Moreover, the changes in the transverse direction may not necessarily be identical to those in the longitudinal direction so that alterations in the shape of the heart may occur. In this context, a spherical configuration corresponds to a condition of minimal and uniform stress distribution while an ellipsoid pattern generates a greater and dissimilar distribution of stress along the myocardial surface and a cylindrical shape is associated with the least advantageous geometry.[37,38] These configurational changes after infarction are still unclear, although they may represent significant variables in the etiology of the dilated cardiomyopathic heart of ischemic origin.

The mechanism of lateral myocyte slippage has previously been inferred in wall thickness changes accompanying variations of ventricular volume in the intact heart in vitro,[13,39] after acute[12] and chronic[11] ventricular dysfunction, as a result of transient but repeated episodes of myocardial ischemia,[40] and during the alterations in loading condition of the heart associated with the transition from the fetal to the adult circulatory system early after birth in the rat.[41] Recently, a similar phenomenon has been suggested to be operative following coronary artery constriction.[35]

## MYOCARDIAL INFARCTION AND CHRONIC VENTRICULAR REMODELING

Having summarized in the preceding section the structural events involved in the acute adaptation of the heart to ischemic myocardial injury, the chronic response of the ventricular myocardium will be discussed here in an attempt to identify how the growth reaction of the unaffected myocytes and their interrelation within the wall participate in the characterization of cardiac anatomy late after infarction.[42] Compensatory hypertrophic mechanisms continue to occur throughout healing and thereafter so that the originally lost myocardium is replaced by fewer enlarged cells.[29] However, the regeneration of ventricular mass may not be capable of normalizing ventricular function and the early ventricular dilation with wall thinning may complicate irreversibly the long-term outcome of myocardial infarction. Moreover, myocyte cellular hypertrophy in the regions bordering and remote from the infarct[43] may not be adequate to restore cell stress within normal limits and this deficiency may be a function of infarct size.

**Ventricular anatomy and wall stress chronically after infarction:** To address the questions raised above, the functional and structural properties of the heart were examined 1 month after coronary artery occlusion, which resulted in infarcts affecting 38% (small infarcts) and 60% (large infarcts) of the free wall of the left ventricle.

Physiologic measurements showed that mean arterial blood pressure was not affected by a 38% infarct, whereas a 60% loss of viable myocardium resulted in a 23% decrease in this parameter. In addition, a 19% difference in mean arterial pressure was measured between the two infarct groups. Large infarcts also produced a 20% reduction in left ventricular systolic pressure, which, however, remained unchanged in rats with small infarcts (Figure 6). Although mean arterial pressure and peak systolic ventricular pressure were not altered by a 38% infarct, left ventricular end-diastolic pressure was found to be increased from 2 to 6 mm Hg. In the presence of a 60% infarct, left ventricular end-diastolic pressure reached a value of 16 mm Hg, which was markedly higher than that measured in control rats and in rats with small infarcts. In addition, estimations of *dP/dt* demonstrated an 8% and a 31% reduction in rats with small and large infarcts, respectively. Large infarcts showed a 25% lower *dP/dt* value than small infarcts.

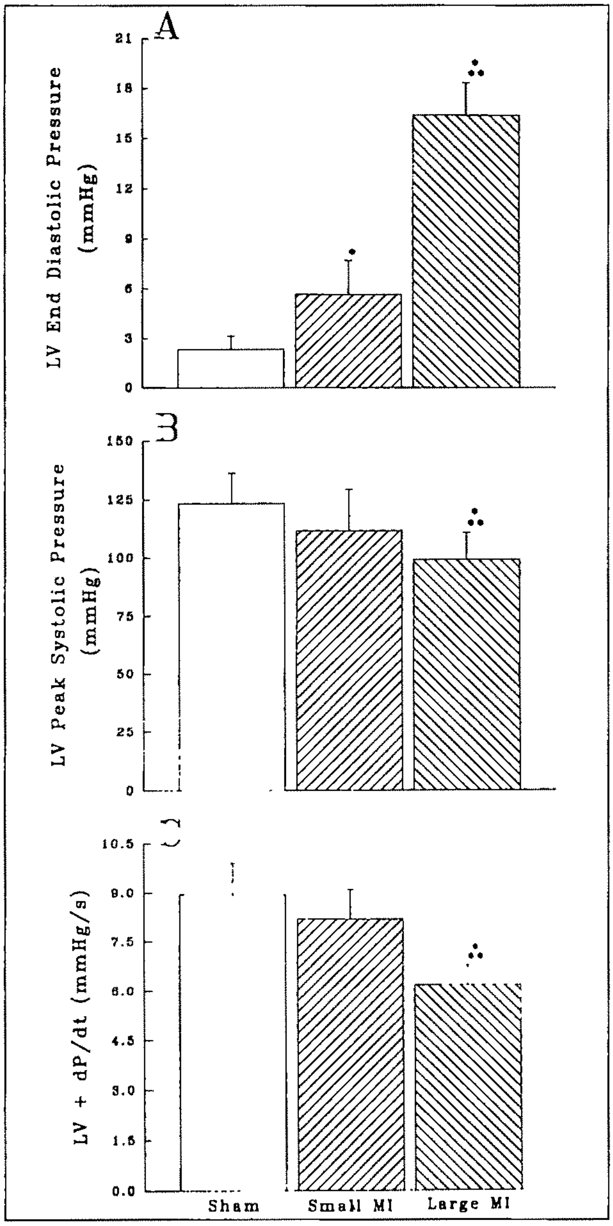

**FIGURE 6. Changes in left ventricular (LV) end-diastolic pressure, left ventricular systolic pressure, and left ventricular dP/dt, 30 days after myocardial infarction (MI). *Significantly different, p <0.05, compared with sham-operated control rats. **Significantly different, p <0.05, compared with rats with small infarcts.**

Figure 7 depicts the changes in transverse chamber diameter and in the thickness of the free wall (border zone) and septum (remote myocardium) as a consequence of myocardial infarction.

One month after coronary artery occlusion, transverse chamber diameter increased by 6% and 27% in rats with small and large infarcts, respectively. Moreover, large infarcts provoked a 20% greater ventricular dilation than small infarcts. Since the thickness of the ventricular wall bordering and remote from the infarct increased by 8% in rats with small infarcts and remained essentially constant in rats with large infarcts, the wall thickness/chamber radius ratios in the border zone and remote myocardium did not vary in rats with small infarcts but markedly decreased in rats with a 60% infarct.

To establish whether the dimensional changes of the infarcted ventricle in combination with the impairment of cardiac hemodynamics resulted in alteration in tension on the surviving myocardium, diastolic stress was computed from the Laplace equation. This parameter increased by 2.4-fold and 2.3-fold in the border and remote regions in rats with small infarcts. In the presence of large infarcts, augmentations of 8.8-fold and 9.3-fold were measured in the zones adjacent and away from the scarred tissue. Moreover, with large infarcts, diastolic stress was nearly 4-fold greater than with small infarcts.

Additional characteristics pertinent to the recognition of the magnitude of ventricular remodeling associated with infarction are illustrated in Figure 8. The major longitudinal axis of the ventricle increased by 11% in rats with large infarcts. Moreover, the computation of chamber volume showed that marked augmentations in ventricular cavity size occurred with infarction. In rats with small infarcts, a 15% expansion in chamber volume was found, but this change was not statistically significant. On the other hand, large infarcts were accompanied by an 81% increase in cavity volume and this chamber enlargement exceeded by 57% the dilation generated by small infarcts. In view of the fact that the volume of ventricular mass constituted by the surviving myocardium of the left ventricular free wall and septum combined decreased by 10% in rats with large infarcts, a 50% reduction in ventricular mass/chamber volume ratio was measured in this case. In rats with small infarcts, a 15% decrease in ventricular mass/chamber volume ratio was found.

In summary, myocardial infarction is associated chronically with ventricular dilation and an increase in left ventricular end-diastolic pressure, which together contribute to a marked elevation in diastolic wall stress. These abnormalities are also a function of infarct size. Thus, diastolic overloading appears to constitute the prevailing hemodynamic alteration in healed myocardial infarction. Since a similar condition has been found acutely,[30] it is tempting to speculate that severe ischemic injury of the myocardium leads to diastolic dysfunction that is not reversed by the hypertrophic reactive process of surviving muscle fibers.[42] Moreover, the expansions in ventricular chamber volume exceed those involving the growth response of the viable myocardium, resulting in a decrease in the mass-to-volume ratio. These anatomic parameters of the infarcted ventricle are consistent with ventricular shape changes characteristic of decompensated eccentric hypertrophy, the form of hypertrophy that distinguishes the transition from compensated pressure and/or volume overload hypertrophy to myocardial dysfunction and failure.[44-50]

**Cell movement and wall and chamber remodeling chronically after infarction:** In an analysis identical to that described acutely after infarction, the changes in myocyte size and shape are discussed first. One month after coronary artery occlusion and small infarcts, myocyte cell volume increased 43% in the border zone and 20% in the zone away from the scarred tissue (Figure 9). After large infarcts, the cellular responses were 81% and 32%. Moreover, cell volume in the group of rats with large infarcts was 26% and 10% greater than that found in the border and remote regions of rats with small infarcts. In the presence of small in-

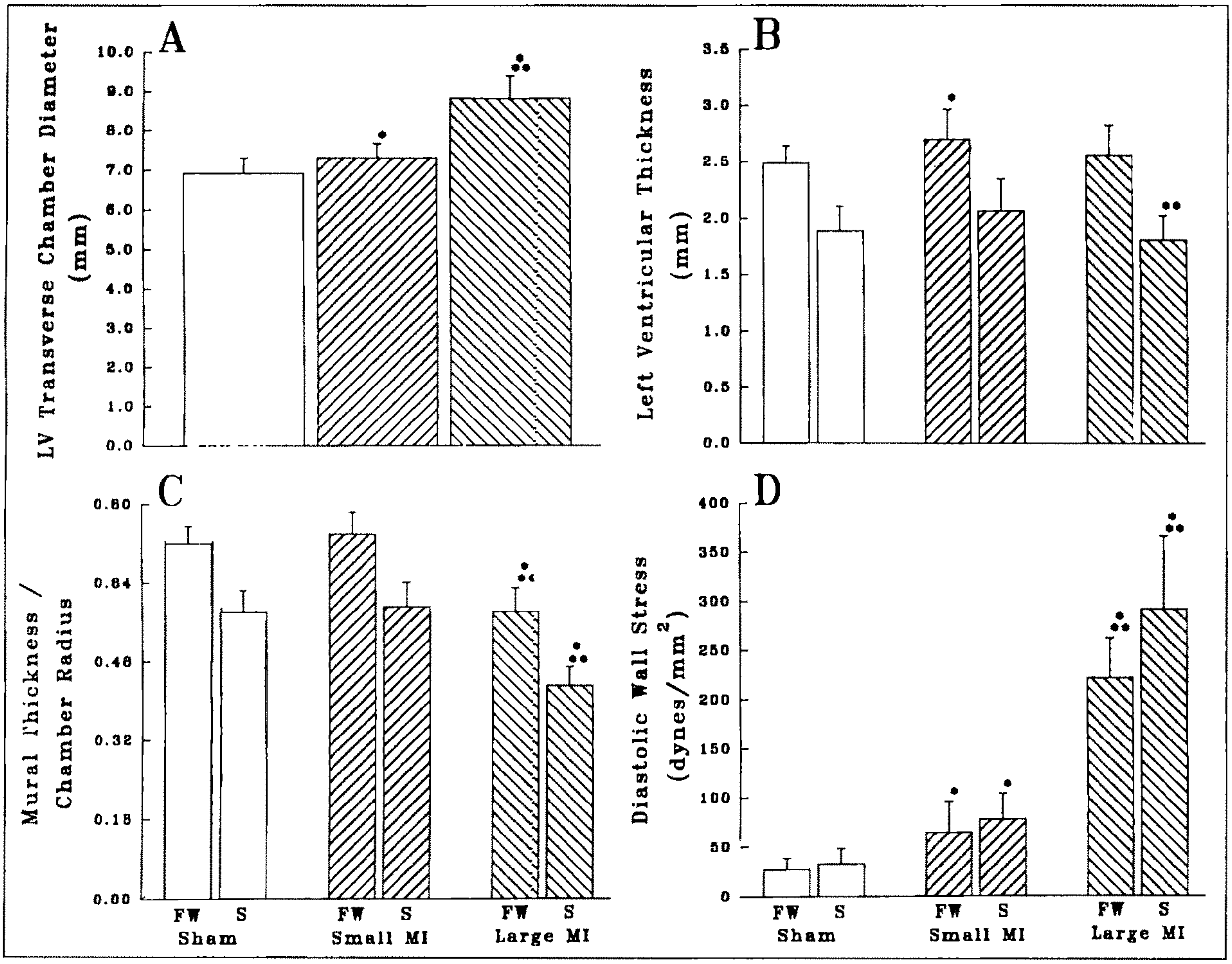

**FIGURE 7. Changes in the characteristics of the chamber of the infarcted left ventricle, thickness of the wall of the unaffected myocardium, and midwall circumferential diastolic stress on the viable tissue, 30 days after myocardial infarction (MI). FW = free wall; LV = left ventricular; S = interventricular septum. *Significantly different, $p < 0.05$, compared with sham-operated control rats. **Significantly different, $p < 0.05$, compared with rats with small infarcts.**

farcts, myocyte hypertrophy in the myocardium adjacent to the scar was produced by a 7% increase in the average diameter and a 25% augmentation in mean length. Corresponding increases in the presence of large infarcts were 17% and 33%. Changes of smaller magnitude were noted in the remote myocardium. Cell lengthening per nucleus averaged 13% and 19% in the presence of small and large infarcts. The lateral expansion of myocytes was 3% and 5%. Finally, as a result of a 60% infarct, the diameter of myocytes in the border zone was 9% greater than that of the corresponding cells adjacent to infarcts comprising 38% of the ventricular wall.

Figure 10 illustrates that 1 month after an infarction resulting in a 60% loss of mass there was a 12% reduction in the average number of myocytes across the region of the wall bordering the fibrotic tissue, despite the fact that wall thickness in this zone of the injured ventricle was similar to that of control hearts. Moreover, the capillary number within the thickness of the wall was also decreased by 14%. In the remote myocardium, both myocytes and capillaries were reduced by 8%. No change occurred in these myocyte and capillary quantities in rats with a 38% infarct.

In summary, chronic cellular growth mechanisms after infarction parallel not only the extent of myocardium lost on an obligatory basis, but also the magnitude of ventricular dilation. Moreover, hypertrophy of the spared myocytes in the region bordering the scarred tissue is greater than that in the portion remote from the infarct, and this difference increases with infarct size.

Importantly, cellular enlargement is characterized by increases in myocyte diameter and length, which are consistent with a phenomenon of concentric and eccentric hypertrophy in the intact ventricular wall.[10] In the presence of large infarcts, an additional structural mechanism is implicated in ventricular dilation and relative wall thinning. The number of myocytes and capillaries across the wall decreases in the border and remote myocardium. Such a phenomenon of side-to-side slippage of

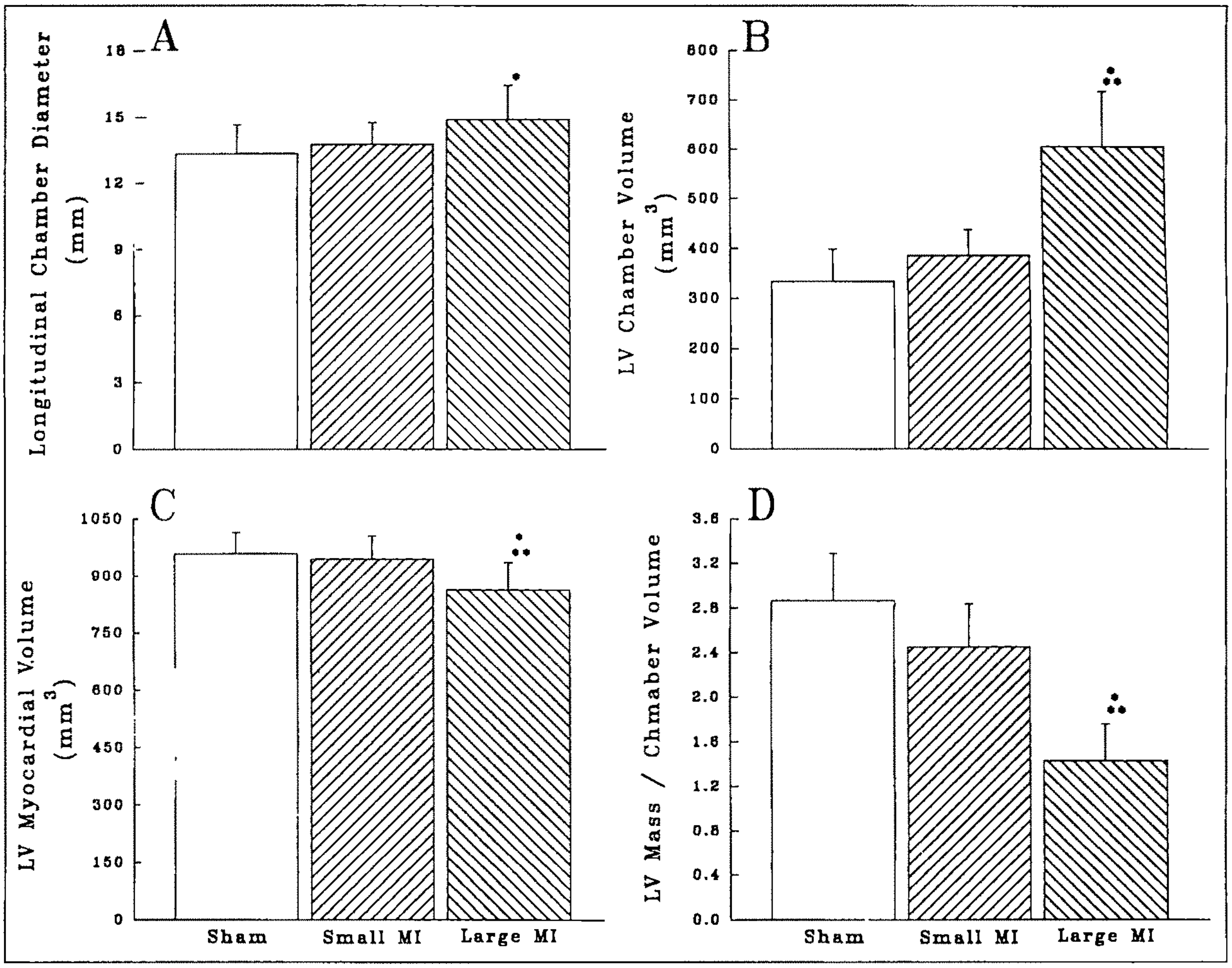

**FIGURE 8. Changes in longitudinal chamber diameter, chamber volume, viable ventricular volume, and their relations 30 days after myocardial infarction (MI). LV = left ventricular. *Significantly different, $p < 0.05$, compared with sham-operated control rats. **Significantly different, $p < 0.05$, compared with rats with small infarcts.**

cells and capillaries within the wall has been shown to be an important factor in the acute dilation of the infarcted ventricle.[30] However, the magnitude of this process is significantly greater in the acute than in the chronic phase of remodeling, raising the possibility of the reversibility of this event. Thus, negative side-to-side slippage of cells with wall thinning early after ischemic injury may be counteracted later during healing by an opposite positive movement of cells and wall thickening. Moreover, muscle fiber slippage appears to be a function of infarct size affecting mostly the border zone of an infarct.

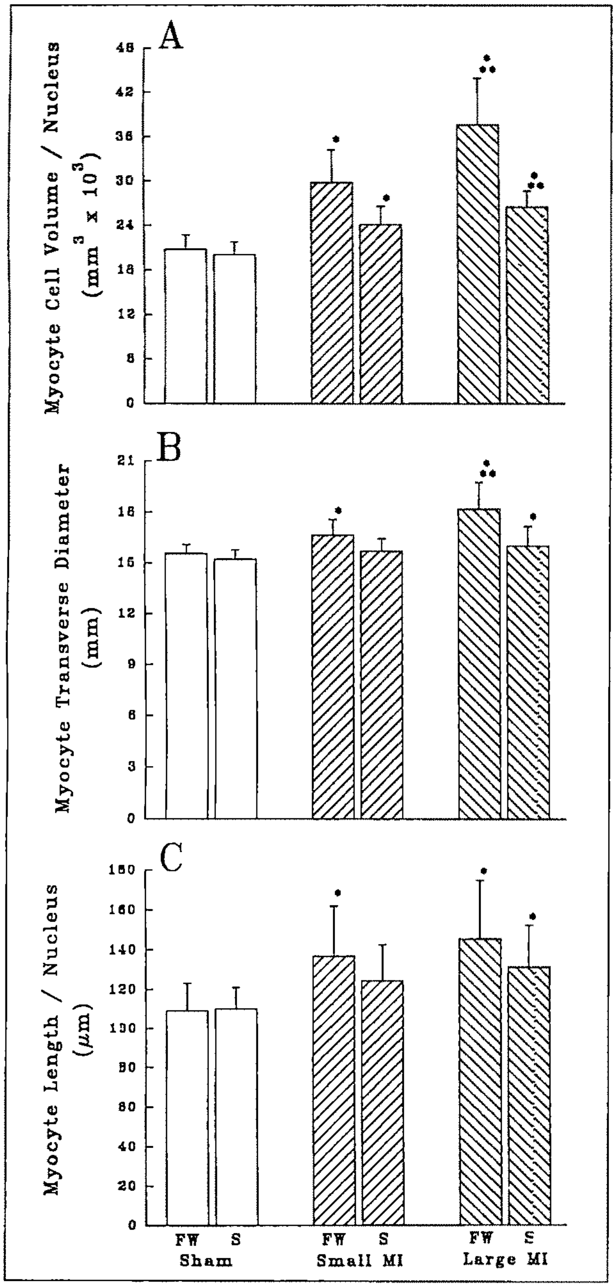

**FIGURE 9. Changes in myocyte cell volume diameter and length per nucleus in the surviving tissue 30 days after myocardial infarction (MI). FW = free wall; S = interventricular septum. *Significantly different, $p < 0.05$, compared with sham-operated control rats. **Significantly different, $p < 0.05$, compared with rats with small infarcts.**

In conclusion, ventricular dilation after infarction occurs through side-to-side slippage of myocytes in the myocardium, which characterizes the acute adaptive response of the injured ventricle, whereas cell lengthening constitutes the prevailing mechanism of chamber enlargement chronically. These two events contribute to the immediate and subsequent elevation in diastolic wall stress, which represents the primary mechanical stimulus for myocyte hypertrophy. However, decompensated eccentric ventricular hypertrophy develops after infarction, and growth processes in myocytes are inadequate for normalization of wall stress when myocyte loss involves nearly 40% or more of the cells of the left ventricular free wall. The persistence of elevated myocardial and cellular loads

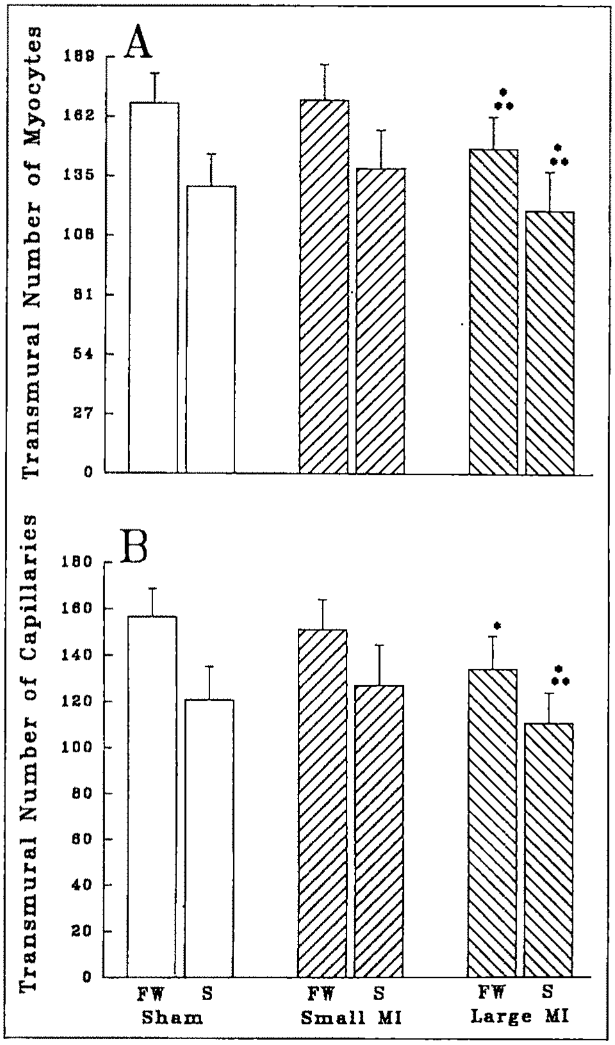

**FIGURE 10. Changes in the number of myocytes and capillaries across the wall of the surviving ventricular myocardium 30 days after myocardial infarction (MI). FW = free wall; S = interventricular septum. *Significantly different, $p < 0.05$, compared with sham-operated control rats. **Significantly different, $p < 0.05$, compared with rats with small infarcts.**

may sustain the progression of the disease state toward end-stage congestive heart failure.

**Acknowledgment:** The excellent assistance of Lucille Robinson is greatly appreciated.

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# Progressive Ventricular Dilation in Experimental Myocardial Infarction and Its Attenuation by Angiotensin-Converting Enzyme Inhibition

Janice M. Pfeffer, PhD

**The extent to which the impaired left ventricle dilates may have important prognostic implications for survival. To determine the influence of infarct size and duration on ventricular dilation, the passive pressure–volume relation of the left ventricle in the rat after coronary artery ligation was obtained. In the early (0.25 to 2 days) phase, the pressure–volume relation was relatively unchanged in all infarct-size groups, except for a rightward shift in the low pressure range for moderate and large infarcts and a leftward shift in the high pressure range for small infarcts. From 2 to 7 days, ventricular dilatation occurred in all groups in relation to infarct size. Thereafter (to 106 days), in rats with moderate and large infarcts, the left ventricle continued to dilate. Associated with this late dilation was a decrease in left ventricular chamber stiffness and an increase in the volume to mass ratio. To determine whether the potentially deleterious progression of ventricular dilation could be attenuated, the angiotensin-converting enzyme inhibitor captopril was given 2 or 21 days after infarction and continued for 3 months. There was a significant overall effect of this treatment in attenuating left ventricular dilation, which was most pronounced in moderate infarcts. Captopril not only attenuated the rightward shift of the pressure–volume relation, but also markedly lowered left ventricular filling pressures so that operating volumes in treated rats were considerably reduced compared with those in untreated rats, even in large infarcts. Therapy with captopril also had an overall effect in prolonging survival, the most benefit being observed in moderate infarcts with lesser dilated left ventricles.**

**(Am J Cardiol 1991;68:17D–25D)**

Left ventricular dysfunction and dilation as a consequence of myocardial infarction may have important prognostic implications for survival. Coronary artery ligation in the rat produces a broad spectrum of ventricular dysfunction, ranging from minimal impairment to overt heart failure, depending on the size of the myocardial infarction. We examined the manner and extent to which the infarcted left ventricle is remodeled (changes in volume and/or mass) during both the early phase of acute myocardial necrosis and inflammation and the later phase of fibrous tissue replacement and histologic healing, or scar formation, and beyond. To determine whether the processes of ventricular remodeling and dysfunction could be altered favorably, the angiotensin-converting enzyme (ACE) inhibitor captopril was administered to rats at either 2 or 21 days following myocardial infarction and continued for 3 months, after which time left ventricular hemodynamics and passive pressure–volume relations were obtained. Since captopril attenuated ventricular enlargement while preserving ventricular performance, this agent was administered to rats with myocardial infarctions and the rats were followed until death or for a period of 1 year to determine the effect of ACE inhibition on survival. These data have been reported in detail elsewhere.[1–3]

## METHODS

**Longitudinal studies:** Myocardial infarctions were produced in 279 female Wistar rats using a previously described technique of coronary artery ligation.[4,5] Left ventricular passive pressure–volume relations were obtained during both the early (0.25, 1, and 2 days) and the late (7, 19, and 106

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days) postinfarction phases by the infusion of saline over a pressure range of 0–30 mm Hg in KCl-arrested hearts.[1,5] The pressure–volume data at every unit of pressure from 2.5 to 30 mm Hg were fitted by a single, 2-constant exponential, $P = be^{kv}$, and the value of $k$ was used as an index of left ventricular chamber stiffness.

The left (plus septum) and right ventricles were dissected free and weighed separately. Hearts were processed for histologic examination by methods appropriate for the age of the infarct.[1] For each histologic section, the lengths of scar (or necrotic tissue) and the circumferences of the endocardial and epicardial surfaces were determined by planimetry and numerically summed separately. The ratio of the sum of scar lengths to the sum of circumferences for each myocardial surface was determined and these 2 ratios were then averaged and expressed in a percentage as infarct size.

**Angiotensin-converting enzyme inhibition and ventricular volume:** The ACE inhibitor captopril (2 g/liter of drinking water), was administered to female Wistar rats either 2 or 21 days following the production of a myocardial infarction and continued for 3 months.[2] Hemodynamic studies were performed in 163 rats in which left ventricular pressures were measured and passive pressure–volume relations were obtained. Infarct sizing was performed as mentioned above.

**Angiotensin-converting enzyme inhibition and survival:** Fourteen days after coronary artery ligation, 302 female Wistar rats were assigned to therapy with either the ACE inhibitor captopril (2 g/liter of drinking water) or tap water, based on a balanced block randomization process stratified for infarct size according to 3 electrocardiographic groups.[3] All animals were followed until death or for a period of up to 1 year. Pathologic evaluations were performed on each animal and the data were censored for thoracic infections. Infarct size was determined by planimetry.

**Statistical analysis:** For the *longitudinal studies,* infarcts were classified, based on the percentage of the left ventricle that was scar, as small (≥5 to <30%) moderate (≥30 to <45%), and large (≥45%). To detect differences between the infarct-size groups and the noninfarcted group at each time interval, a 1-way analysis of variance (ANOVA) (with Dunnett's test for 3 comparisons) was performed, and to detect differences that occurred over time within each infarct-size group, a 1-way ANOVA (with Duncan's multiple-range test) was performed for each group. For the *ACE inhibition and ventricular volume studies,* Student's $t$-test demonstrated no differences in the data between the groups in which therapy was initiated at 2 or 21 days, and, therefore, the data were pooled. Rats with infarcts were classified as small (≤20%), moderate (>20 to <40%), large (≥40 to ≤45%), and extensive (>45%). For within-treatment comparisons to the noninfarcted group, a 1-way ANOVA (with Bonferroni's $t$-statistic for 4 preplanned comparisons) was performed, and for between-treatment comparisons at a given infarct size, a Student's $t$-test was performed. A random effects model was employed to examine the overall effect of treatment on the pressure-volume relations of all rats with infarcts. In the *ACE inhibition and survival study,* rats with infarcts were classified as small (≥5 to <20%), moderate (≥20 to <40%), and large (≥40%). Log rank tests were conducted to determine: whether infarct size altered survival in the untreated group, whether treatment influenced survival overall, and in which infarct-size group treatment altered survival.

## RESULTS

**Longitudinal studies:** The ratio of left ventricular weight to body weight did not change with time in rats without infarcts or with small infarcts (Figure 1). In rats with moderate and large infarcts this ratio increased in the early postinfarction phase of inflammation and edema, then declined during the formation of a discrete scar from 7 to 19 days as tissue was resorbed, but returned to normal values by 106 days postinfarction, presumably reflecting compensatory hypertrophy of the residual myocardium.[6–8]

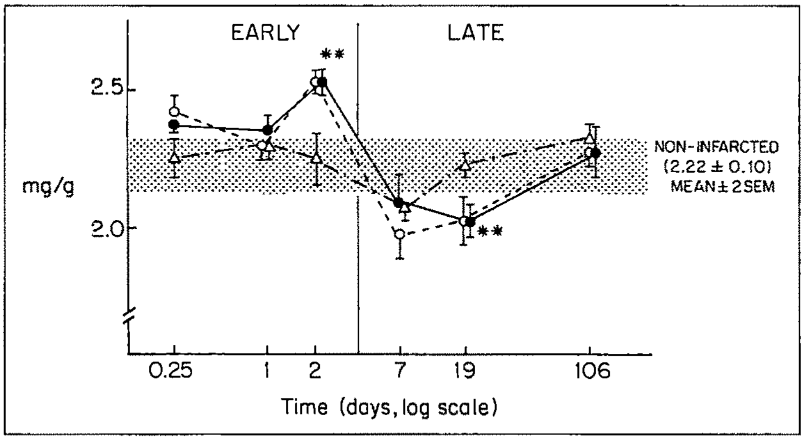
Left ventricular dilation occurred in all infarct-size groups and was related to both the size and duration of infarction (Figure 2). To define more fully the changes that occurred both over time and between groups at each time, volumes were analyzed at both low (2.5 mm Hg) and high (20 mm Hg) filling pressures. In the early postinfarction phase, changes in volume occurred in all infarct-size groups, but at different filling pressures (Figure 3A,B). Left ventricular cavitary volume at 2.5 mm Hg represents the size of the minimally deformed chamber, since filling is associated with distension of the scar from the collapsed state with minimal stretching of the myocardium. Changes in volume at this low filling pressure during the early postinfarction phase are primarily the result of the regional remodeling of the wall of the infarcted area due to infarct expansion.[9,10] These filling volumes at 2.5 mm Hg did not change in rats with small infarcts but were significantly increased in rats with moderate and large infarcts compared with controls (Figure 3A). Indeed, as early as 6 hours postligation, these volumes were already increased by 50% in large infarcts and by 1 day were increased to the same extent as well in moderate infarcts. These larger volumes in the very early postinfarction phase are associated with a mechanical disadvantage to the ventricle because their presence is due to the repetitive bulging of the infarcted region during systole.

The cavitary volumes at high (20 mm Hg) distending pressures reflect changes that occur in both the infarcted region and the residual myocardium. Whereas the volumes at 2.5 mm Hg were unchanged in small infarcts and increased in moderate and large infarcts, the volumes at 20 mm Hg (Figure 3B) were decreased in small infarcts and unchanged in moderate and large infarcts, reflecting a relative leftward shift of these curves at higher pressures. These seemingly contradictory phenomena may be explained by the presence of hypoxic, hypercontracted sarcomeres in the infarcted and peri-infarcted regions[11-13] and by the restraining influence of a stiff aneurysm on the deformation of adjacent fibers,[14] effects that dominate at higher filling pressures and that permit volumes at 20 mm Hg to be reduced in small infarcts and unchanged in moderate to large infarcts in which these restraining influences offset the already increased basic size of the left ventricular chamber.

The aforementioned changes in cavitary volume and the pathologic changes in both the necrotic region and the residual normal myocardium influence the compliance characteristics of the left ventricular chamber. We determined the slope, *k*, of the log pressure versus volume per kilogram relation to provide an index of chamber stiffness, a measure of the resistance of the left ventricle to filling. Although chamber stiffness was increased for all infarct-size groups in the early postinfarction phase (Figure 3C) compared with the late phase (Figure 4C), *k* was not different compared to controls. The volume changes that occurred in the early postinfarction phase were associated with changes of similar magnitude in mass, so that the volume-to-mass ratio also remained unchanged (Figure 3D).

Changes in left ventricular volumes, chamber stiffness, and the volume-to-mass ratio were quite striking in the late postinfarction phase. The cavitary volumes at 2.5 mm Hg increased from 2 to 7 days postligation in all infarct groups according to size, but did not change further thereafter in small infarcts, yet continued to increase with time in moderate and large infarcts (Figure 4A). As scar began to form during this 2- to 7-day period, cavitary volumes at high (20 mm Hg) distending pressures also increased in all infarct groups in relation to size, becoming 15, 26, and 47% greater than controls for small, moderate, and large infarcts, respectively (Figure 4B). In contrast to the increased volumes due to infarct expansion during the early postinfarction phase, these volumes, the result of the remodeling of the residual myocardium, provide a mechanical advantage to the infarcted heart by permitting it to deliver its stroke volume with a decrease in the required extent of circumferential fiber shortening. Throughout the later (7 to 106 days) postinfarction phase, cavitary volumes at 20 mm Hg did not change in rats with small infarcts, but continued to increase in rats with moderate and large infarcts, becoming 79% and 110% greater than controls, respectively. When the operating volumes (cavitary volumes at in vivo filling pressures) of the various infarct-size groups were compared to controls at 106 days,[2] even more marked differences in volume were shown: volumes were more than twice normal in moderate infarcts and more than 4 times normal in large

**FIGURE 1. The ratio of left ventricular weight to body weight during the early and late postinfarction phases. The shaded area represents the mean value ± 2 average standard error of the mean for this ratio in rats without infarcts, small infarcts (△–·–△), moderate infarcts (○----○), and large infarcts (●—●). *p < 0.05, infarct group compared with time-matched group without infarcts.**



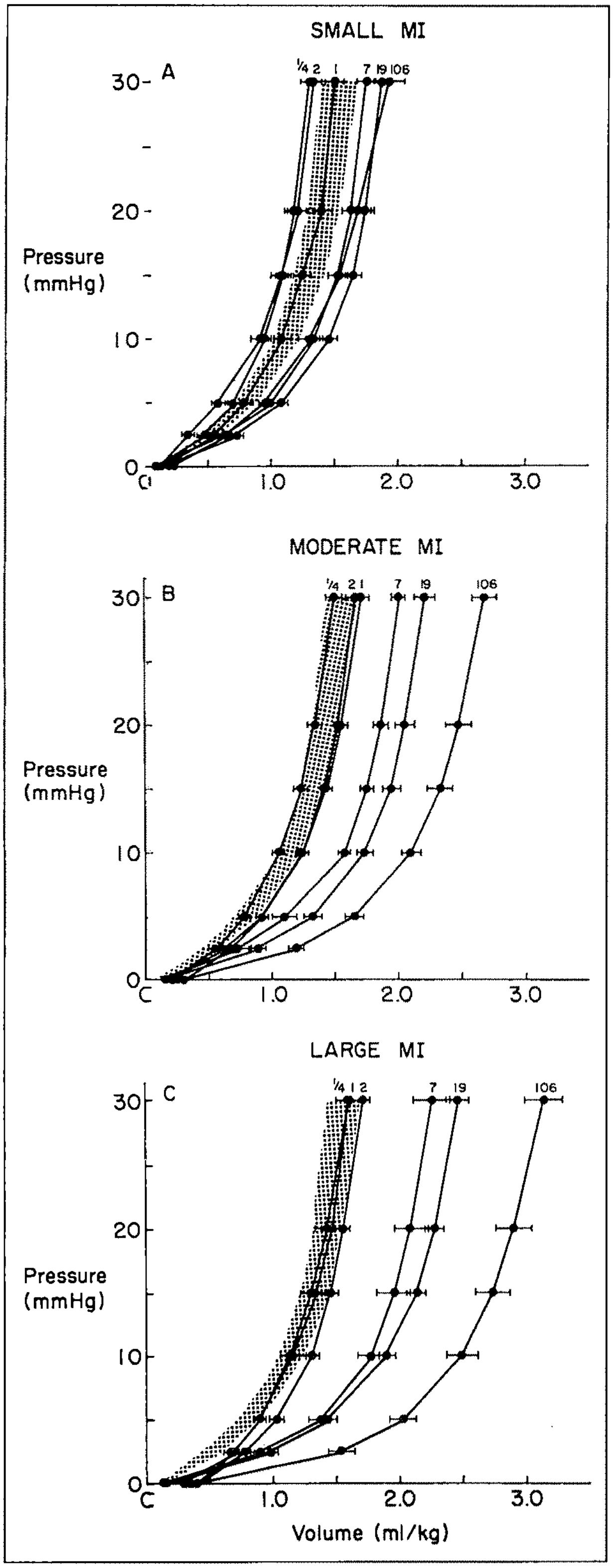


**FIGURE 2. The left ventricular pressure-volume relations of rats with small *(A)*, moderate *(B)* and large *(C)* infarcts during the early and late postinfarction phases. The shaded area represents the mean value ± 2 average standard error of the mean for volume at each level of pressure in rats without infarcts. The time in days postinfarction appears above each curve. (Reprinted with permission from *Am J Physiol.*[1])**

infarcts. This degree of dilatation, however, may be mechanically disadvantageous to the infarcted left ventricle if its shortening load is sustained or increased throughout ejection as chamber volume is reduced relatively little while ventricular pressure is increasing.[15]

These striking changes in cavitary volume that took place during scar formation and beyond had a major influence on the compliance characteristics of the left ventricle. As ventricular dilation occurred, chamber stiffness began to decrease (Figure 4C), becoming significantly less than controls by 19 days in rats with large infarcts and by 106 days in rats with moderate infarcts. The manner by which chamber stiffness can be reduced in a left ventricle with a large nondistensible scar may be explained by the relationship between chamber and myocardial stiffnesses derived by Mirsky et al[16] in which chamber stiffness is directly proportional to myocardial stiffness and inversely proportional to cavitary volume and the cavitary volume to wall volume ratio: $P/V \simeq 4/9 \cdot (E/V)/(1 + V/V_w)$. From 2 to 19 days postinfarction, there was a marked increase in the volume-to-mass ratio (Figure 4D) to which chamber stiffness is inversely related. During this time left ventricular cavitary volume increased (Figure 4A,B) while mass decreased (Figure 1) in moderate and large infarcts, permitting chamber stiffness to be reduced. Despite a return of mass toward normal values by 106 days, the increase in volume was out of proportion to mass so that their ratio increased and chamber stiffness declined even further.

Alterations in the volume-to-mass ratio at a common distension pressure reflect, as well, relative changes in end-diastolic wall stress. At both low (2.5 mm Hg, not shown) and high (20 mm Hg, Figure 4D) distending pressures, this ratio was increased by 7 and 19 days postligation in all infarct-size groups as cavitary volume increased and mass decreased. Both cavitary volume and mass increased thereafter (to 106 days) so that this ratio now was normal in small infarcts, but volume increased disproportionately to mass in moderate and large infarcts and sustained the elevation of this index of diastolic wall stress, suggesting that the stimulus to further volume enlargement was still present.

**Angiotensin-converting enzyme inhibition and ventricular volumes:** To determine whether ACE inhibition could alter favorably the relation between infarct size and ventricular performance and remodeling, we initiated therapy with captopril

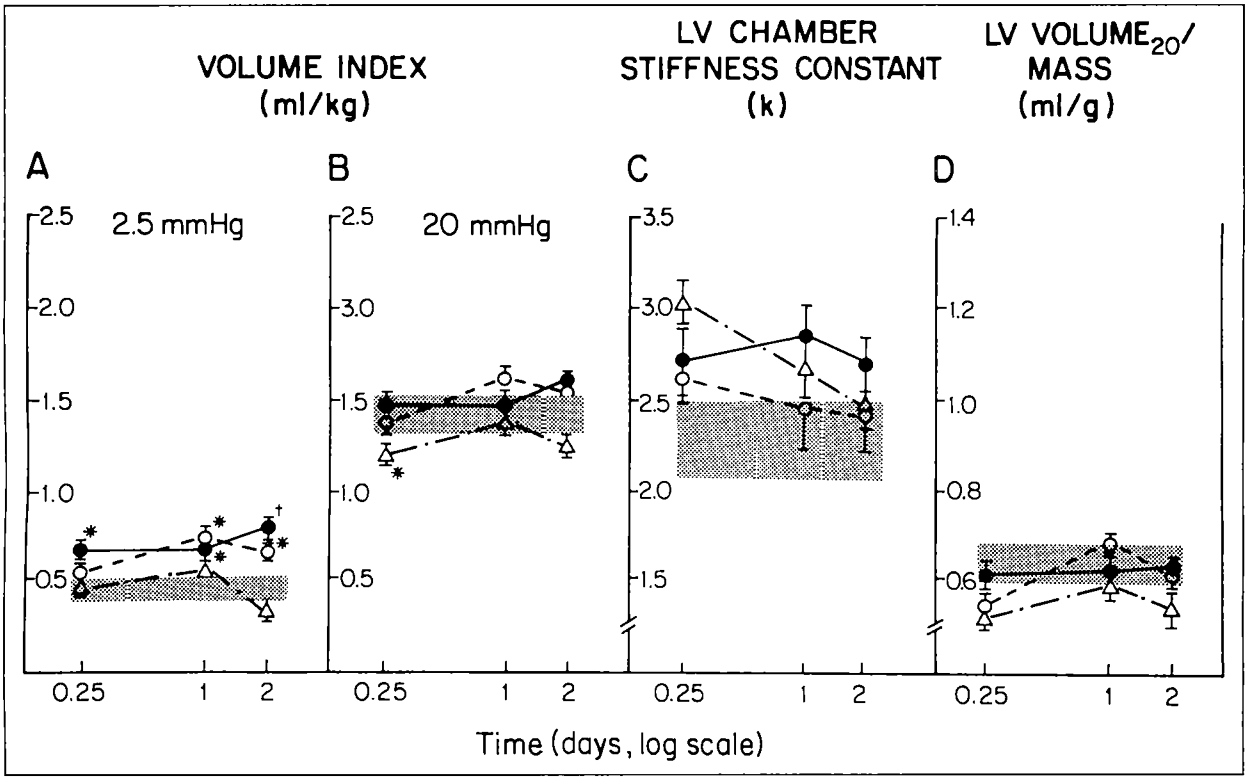


**FIGURE 3. Left ventricular volume-related variables during the early postinfarction phase. Left ventricular diastolic volumes at low (2.5 mm Hg; *A*) and high (20 mm Hg; *B*) filling pressures; chamber stiffness constant (k; *C*); and the ratio of volume at 20 mm Hg to mass (*D*). The shaded area represents the mean value ± 2 average standard error of the mean for each variable in rats without infarcts, small infarcts (△-·-△), moderate infarcts (○----○), and large infarcts (●—●). $^*p < 0.05$, $^\dagger p < 0.01$, infarct group compared with time-matched group without infarcts. (Adapted from data in *Am J Physiol.*[1])**

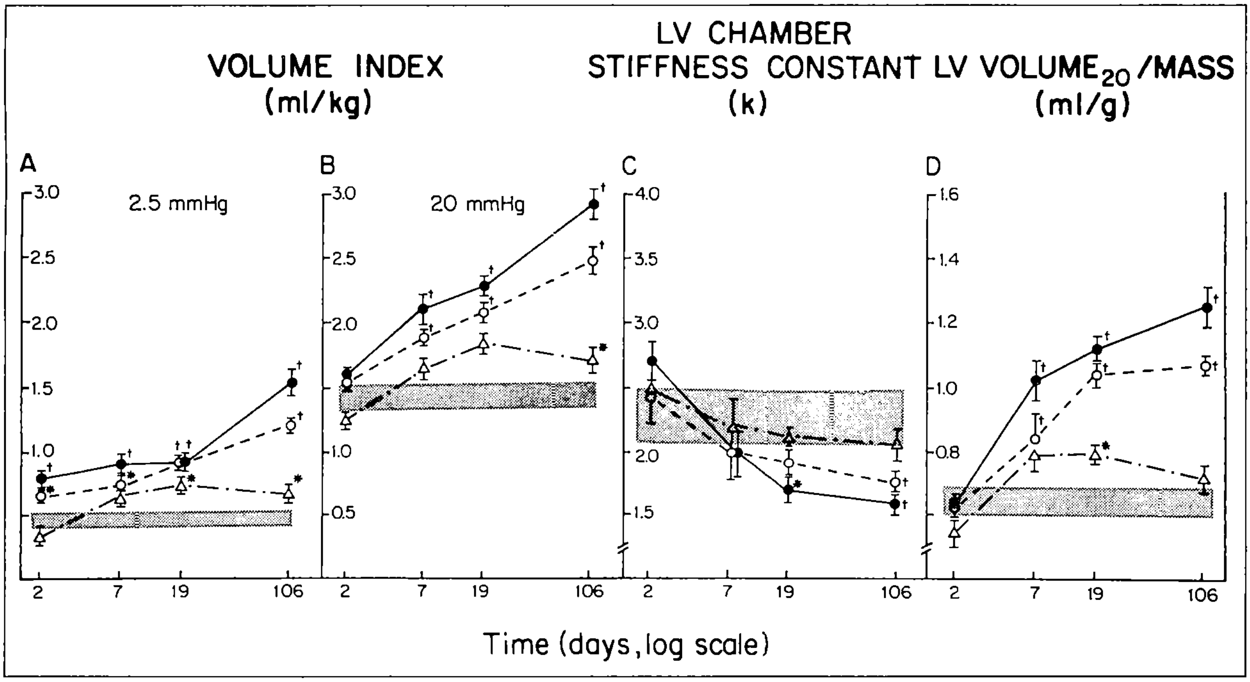


**FIGURE 4. Left ventricular volume-related variables during the late postinfarction phase. Left ventricular diastolic volumes at low (2.5 mm Hg; *A*) and high (20 mm Hg; *B*) filling pressures; chamber stiffness constant (k; *C*); and the ratio of volume at 20 mm Hg to mass (*D*). The shaded area represents the mean value ± 2 average standard error of the mean for each variable in rats without infarcts, small infarcts (△-·-△), moderate infarcts (○----○), and large infarcts (●—●). $^*p < 0.05$, $^\dagger p < 0.01$, infarct group compared with time-matched group without infarcts. (Adapted from data in *Am J Physiol.*[1])**

during both the early (2 days) and late (21 days) postinfarction phases and continued it for 3 months. In untreated rats at 106 days postinfarction, left ventricular end-diastolic pressure increased progressively from 5 to 28 mm Hg in a nonlinear fashion in relation to infarct size. Three months of treatment with captopril maintained filling pressures within normal limits in all infarct-size groups, except for those with extensive infarcts in which, nonetheless, end-diastolic pressure was reduced from 28 to 15 mm Hg.[2] Examination of the effect of this ACE inhibitor on the passive pressure–volume relations, comparing all treated rats to all untreated rats using a random effects model, revealed a significant overall effect of treatment in reducing ventricular volume for any given pressure. The distribution of that benefit of therapy on the pressure–volume relation according to infarct size is shown in Figure 5. For all of the infarct-size groups, captopril produced a leftward shift of the pressure–volume curve. This effect was significant and most dominant in the moderate infarcts (upper panel) and, although still present in large (middle panel) and extensive (lower panel) infarcts, was not significant, the difference between the volumes of the treated and untreated rats becoming less with increasing infarct size. When these 2 beneficial effects of the ACE inhibitor (a lowering of filling pressure and an attenuation of ventricular dilation) were taken into account, the operating volumes obtained were reduced from 1.9 to 1.4 ml/kg in moderate infarcts (upper panel), from 2.2 to 1.6 ml/kg in large infarcts (middle panel), and from 3.1 to 2.6 ml/kg in extensive infarcts (lower panel). Acting in concert, these preload and afterload reducing properties (decreases in ventricular volume and pressure) of captopril temper the mechanical disadvantage that excessive dilation confers on the infarcted left ventricle in that the systolic force required to eject blood is decreased and the extent of circumferential fiber shortening is increased, permitting forward output to be maintained despite the lesser cavitary volume.[2] Indeed, the ejection fraction index of captopril-treated rats was greater than that of untreated rats with moderate infarcts (52% vs 41%) and large infarcts (42% vs 28%).[2]

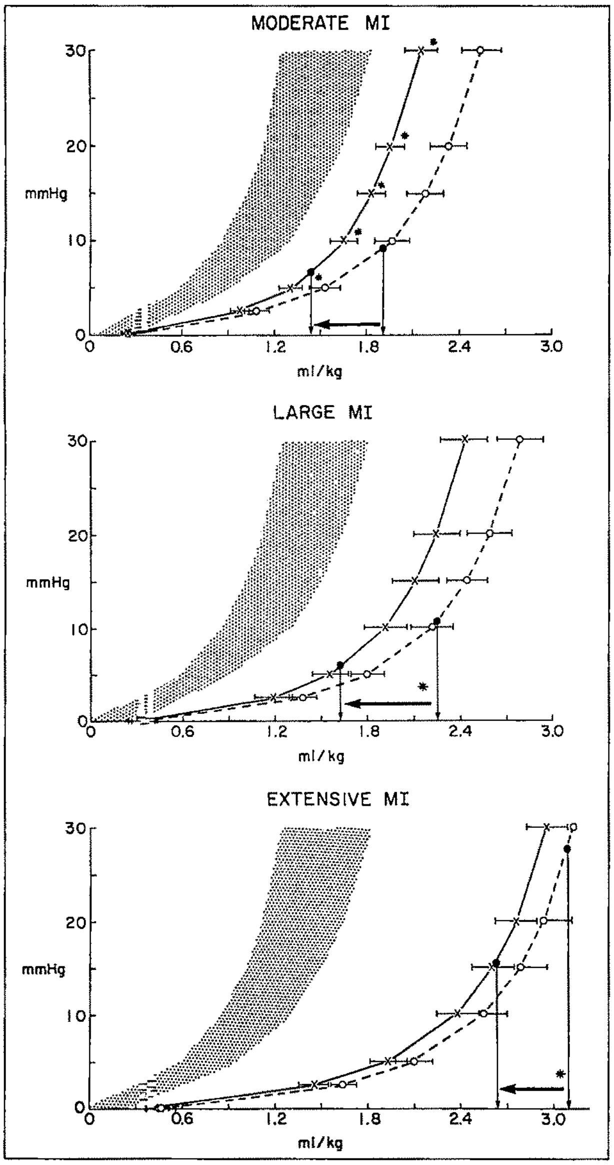


**FIGURE 5. The pressure-volume (per kg) relation of untreated (O) and captopril-treated (X) rats with moderate *(upper panel)*, large *(middle panel)*, and extensive *(lower panel)* infarcts. The shaded area in each panel represents the volumes ± 2 standard deviations of the noninfarcted controls. The vertical arrows in each panel indicate the baseline operating volumes (per kg) of the treated and untreated rats for each infarct-size group. *p $<0.05$, untreated versus treated rats at comparable infarct size for baseline operating volume index. (Modified from *Circ Res.*[2])**

**Angiotensin-converting enzyme inhibition and survival:** Ventricular dysfunction and dilation, irrespective of etiology, portends a poor prognosis.[17] To examine the effects of infarct size, and, thereby, various degrees of left ventricular dysfunction and dilation on survival, rats were followed until death or for up to 1 year postinfarction. As anticipated, survival was inversely related to infarct size: the median survival was greater than 365 days for noninfarcted controls, 360 days for small infarcts, 228 days for moderate infarcts, and 146 days for large infarcts (Figure 6).

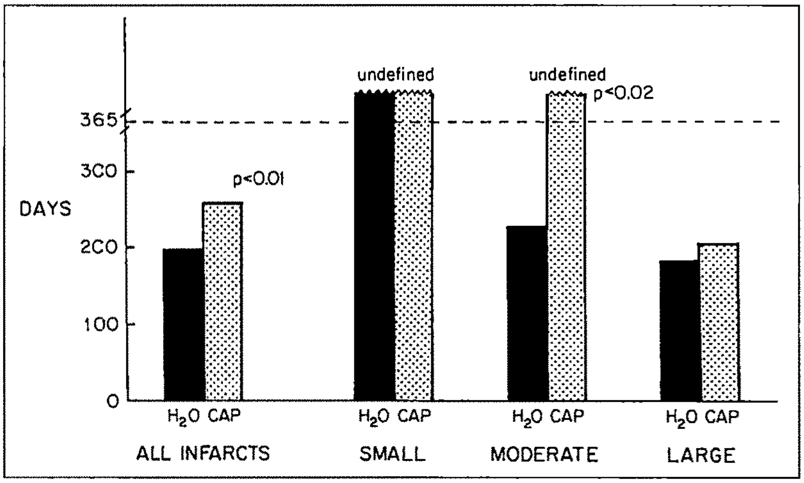
To determine whether the salutary benefits of ACE inhibition on left ventricular hemodynamics and volumes have a positive impact on survival, rats treated with captopril were also followed until death or for up to 1 year postligation.[3] For rats without infarcts, survival was similar between the treated and untreated groups. However, when all rats with infarcts were compared for a treatment effect, captopril significantly reduced mortality rate: the median survival for the untreated rats was 197 days, whereas that for the captopril-treated rats was 260 days (Figure 6). The most pronounced benefit on survival was observed in rats with moderate infarcts: the median survival for untreated rats was 228 days, whereas that for treated rats was greater than 365 days. At 1 year the survival rate in this group of rats with moderate infarcts treated with the ACE inhibitor was more than twice that of the untreated group, 49% vs 21%. Of note is our prior finding that the most beneficial effects of therapy on ventricular hemodynamics and remodeling were observed in rats with moderate infarcts.[2] In rats with large infarcts the median survival without treatment was 184 days, whereas that with treatment was 205 days, a difference that was not significant.

## DISCUSSION

The structural remodeling of the left ventricle following a discrete loss of myocardium due to infarction is a dynamic time-dependent process throughout which changes occur in both the region of necrosis and the residual normal myocardium (Figure 7). The multiple processes of reparation (tissue resorption and scar formation), adaptation (volume enlargement), and restoration (myocyte hypertrophy) contribute interdependently to the reconstruction of the infarcted left ventricle, yet each is dominant at a different phase of the remodeling. During the very early (within 2 days) postinfarction phase of necrosis, edema, and vascular congestion, the left ventricle with a moderate-to-large infarct dilates as a consequence of infarct expansion (a volume increase at low filling pressures) and the free wall thins due to myocyte slippage. Ventricular dilation during this early phase provides no mechanical advantage to the compromised ventricle because its presence is due to the repetitive mechanical deformation of the noncontracting region of necrosis during systole. From 2 to 7 days postinfarction, the reparative process of scar formation begins as necrotic tissue is absorbed and a collagen network is laid down. The infarcted wall continues to thin and elongate and begins to stiffen, but now changes in the residual myocardium also take place, contributing as well to further ventricular enlargement. The restorative process of myocyte hypertrophy (an increase in cell diameter and length) takes place in the noninfarcted wall, permitting dilation (in this instance an adaptive process) to provide the compromised ventricle with a mechanical advantage by restoring stroke volume with a decrease in the required extent of circumferential fiber shortening. From 7 to 19 days postinfarction, a discrete thin scar is formed and the ventricle enlarges further as changes in the residual myocardium continue. After the healing process is complete, ventricular dilation may proceed unabated despite continued hypertrophy of the residual myocardium. The stress that cavitary dilation (an increased radius) places on an inadequately hypertrophied wall of residual myocardium may provide an unrelenting stimulus to further ventricular dilation, which may now place the infarcted ventricle at a mechanical disadvantage. A substantially enlarged (2- or 3-fold) ventricle may sustain, or even increase, its shortening load throughout ejection because chamber volume is reduced relatively little while ventricular pressure is increasing.

Administration of the ACE inhibitor, captopril, during the early postinfarction phase (2 days, a time by which infarct expansion has already oc-

**FIGURE 6. The median survival in days for untreated ($H_2O$, solid bar) and captopril-treated (CAP, stippled bar) rats followed until death or for a period up to 1 year postinfarction. Median survivals greater than 365 days were termed undefined. $p < 0.01$, $p < 0.02$, treated versus untreated rats within each infarct classification.**



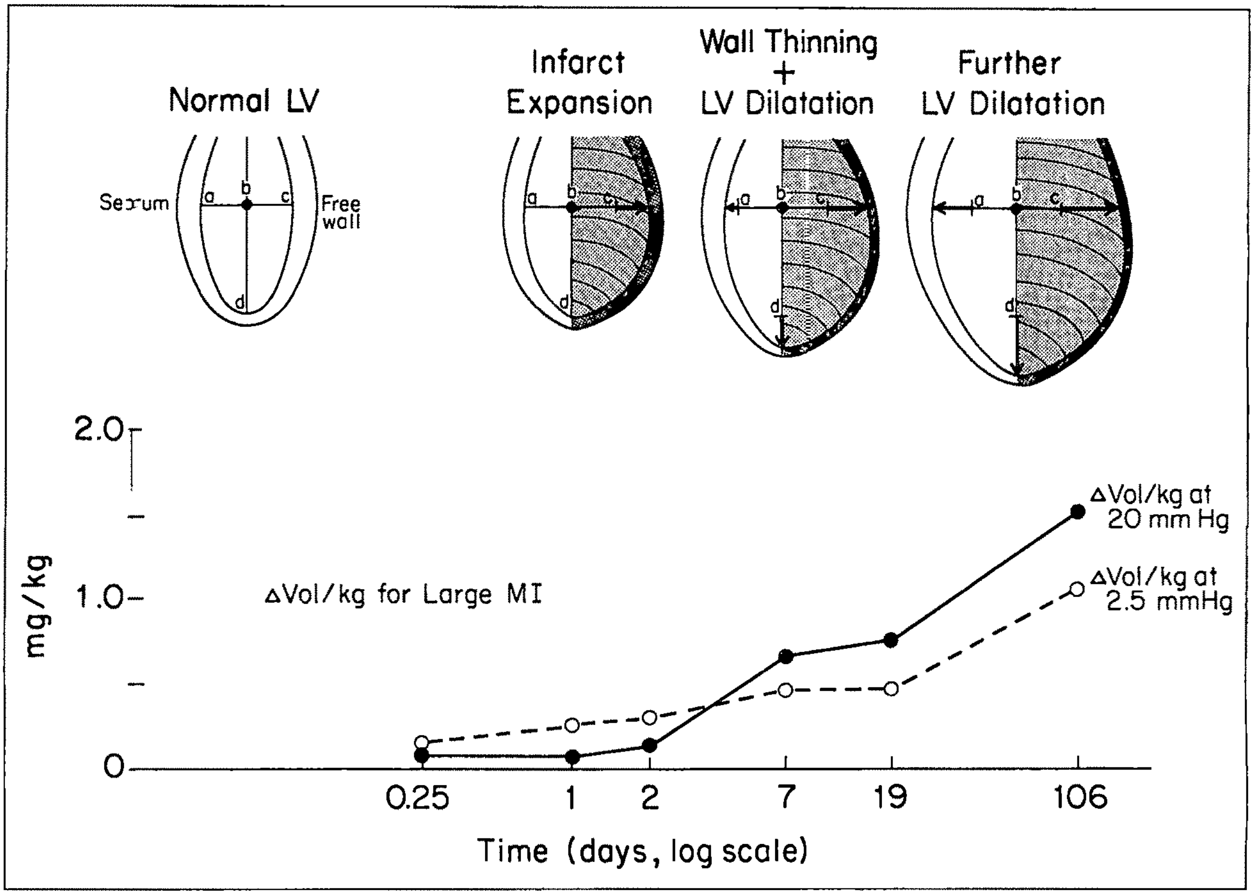


**FIGURE 7. Schema of volume changes occurring in the left ventricle (LV) during the early and late postinfarction phases. In the normal left ventricle the lengths ba and bc represent the distance (minor radius) from the midpoint of the left ventricle to the septum and free wall, respectively; the length bd represents the distance (major radius) from the midpoint to the apex. These distances are presented in the infarcted left ventricles as a frame of reference. The directional arrows attached to the normal radii illustrate the extent of and the regions involved in volume changes during the various postinfarction phases, but are not drawn to scale. The shaded area represents an infarction comprising 50% of the surface area of the left ventricle. The graph in the lower portion of the figure depicts the net increase in absolute volume per kilogram for ventricles with large-sized infarcts compared with ventricles without infarcts. MI = myocardial infarct.**

curred) or late postinfarction phase (21 days, a time by which scar formation is complete and ventricular dilation due to changes in the residual myocardium has already occurred) interrupted the development of severe left ventricular dysfunction and dilation. Treatment with captopril acted in 2 ways to reduce ventricular volumes: by less ventricular distension, i.e., a downward displacement on the pressure–volume relation as the result of a lowering of filling pressure, and by less ventricular dilation, i.e., an attenuation of the time-dependent rightward shift of the pressure–volume relation. This reduction in distending pressure and prevention of the deleterious remodeling (excessive dilatation) of the infarcted left ventricle by ACE inhibition abbreviated the mechanical disadvantage conferred by severe ventricular enlargement, that is, the load on the heart was no longer sustained or elevated, but was reduced throughout ejection.

These laudatory effects of ACE inhibition on ventricular hemodynamics and remodeling in rats with experimental myocardial infarction were translated into a prolongation of survival. Captopril reduced the mortality rate of all rats with infarcts, but did so most effectively in moderate infarcts, those in which ventricular performance was preserved and ventricular dilatation was attenuated. Currently, several clinical trials are underway to determine whether the same salutary benefits of ACE inhibition that have been demonstrated experimentally will be observed in man.

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# Effects of Captopril on Contractility After Myocardial Infarction: Experimental Observations

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**After large myocardial infarction, compromised left ventricular (LV) function and changes in the peripheral circulation result in the syndrome of chronic congestive heart failure. Although treatment with angiotensin-converting enzyme inhibitors improve cardiovascular function, it is difficult to determine whether this benefit is due to changes in organ versus muscle function. The rat model of heart failure, created by ligating the left coronary artery, results in pathophysiology that is similar to that seen in patients, i.e., increased LV end-diastolic pressure and volume, hypertrophy of the noninfarcted myocardium, prolongation of the time constant of LV relaxation, decreased venous compliance, and increased total blood volume. In noninfarcted papillary muscles, isolated from rats with heart failure, maximal developed tension and peak rate of tension rise (+*dT/dt*) are decreased, time to peak tension is prolonged, and myocardial stiffness is increased. Morphologic changes include an increase in papillary muscle myocyte cross-sectional area and an increase in myocardial hydroxyproline content. Captopril (2 g/liter drinking water) alters LV loading by decreasing arterial pressure, increasing venous compliance, and decreasing blood volume. This results in a decrease in LV end-diastolic pressure and volume. In the noninfarcted myocardium, time to peak tension is shortened, whereas developed tension, +*dT/dt*, and muscle stiffness remain abnormal. Captopril decreases myocyte cross-sectional area, but collagen content remains elevated. Thus, in the rat infarct model of heart failure, treatment with captopril alters LV remodeling and hypertrophy but produces only modest improvement in muscle function. In this model, after treatment for 3 weeks, it appears that the major benefit from angiotensin-converting enzyme inhibition is due to improvements in organ function resulting from changes in loading conditions, whereas muscle function remains compromised.**

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Large myocardial infarction frequently produces progressive left ventricular (LV) dilation and hypertrophy of myocytes in the noninfarcted myocardium. These changes in LV geometry, referred to as LV remodeling, may contribute to development of the syndrome of chronic congestive heart failure. Laboratory and clinical studies have shown that treatment of heart failure with angiotensin-converting enzyme (ACE) inhibitors, such as captopril, can improve LV function and survival.[1-9] Although it is commonly believed that the beneficial effects of captopril are due to improvement in ventricular loading conditions, this explanation may be too simplistic. We hypothesized that following large myocardial infarction, functional impairment of noninfarcted myocardium would occur due to the increased load borne by the residual myocytes. Unloading these myocytes might be expected to result in a gradual improvement in their function. Because of the complex effects of simultaneous changes in myocardial function, ventricular geometry, and ventricular–vascular coupling on global LV function, it is difficult to assess the relative importance of changes in each area. This report focuses on our efforts to

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separate alterations in muscle function from those in organ function and how captopril affects each of these in rats with heart failure.

It is difficult to evaluate intrinsic myocardial function following myocardial infarction by measuring global ventricular function because these indexes of function represent the net change in the residual noninfarcted myocardium and in the scar. For example, it is important to define changes in wall stress to understand alterations in both systolic and diastolic function. Traditional methods of measuring myocardial wall stress in vivo rely on mathematical models that assume that the ventricle has symmetrical shape, uniform wall thickness, homogeneous myocardial elasticity, and a constancy of forces from epicardium to endocardium.[10] These assumptions cannot be applied to the infarcted heart. Therefore, to investigate this problem in the research laboratory, we chose to perform studies using isolated myocardial tissue as well as intact rats to evaluate adequately the effects of ACE inhibition on ventricular loading conditions and myocardial mechanics.

Our unifying hypothesis in these studies was that activation of systemic or tissue renin–angiotensin systems may play a key role in the sequence of events leading to heart failure. Because of direct myocardial effects of angiotensin II, such as trophism and inotropism, in addition to its effects on the peripheral circulation, we reasoned that blocking the production of angiotensin II might interrupt or slow the process of LV remodeling and the development of heart failure after myocardial infarction. We hypothesized that the effectiveness of captopril in improving organ function is dependent on its ability to cause both arterial and venous dilation. We also hypothesized that myocardial infarction would result in depressed contractility and increased muscle stiffness in the noninfarcted myocardium. We speculated that treatment with captopril would partially reverse these abnormalities, since these parameters were, at least in part, load dependent.

## METHODS

All studies described in this article conformed to the animal care guidelines of the American Physiological Society. Myocardial infarction was produced in male Sprague-Dawley rats (Harlan, Indianapolis, IN) weighing 220–260 g, by ligation of the proximal left coronary artery.[11–13] Rats were screened for evidence of large myocardial infarction 21 days after surgery using surface electrocardiographic (ECG) recording. Previous studies have shown that most rats identified in this manner have infarction of greater than 40% of the left ventricle, elevated LV end-diastolic pressure and volume, and impaired systolic function.[8,9,13–15]

Rats with large infarctions and sham-operated rats were randomly assigned to no treatment or treatment with captopril (2 g/liter; ER Squibb, Princeton, NJ). Treatment with captopril was started 21 days after surgery and was continued for 21 days. This time course was chosen because histologic healing of the infarct region is complete at 21 days.

To obtain pressure measurements, the rats were anesthetized with methoxyflurane, and a micromanometer-tipped catheter (Millar Instruments, Houston, TX) was inserted into the right carotid artery. The catheter was advanced into the aorta and then into the left ventricle for recording of pressures. With the rat lightly anesthetized and breathing spontaneously, recordings were made on a physiologic recorder (model 2400, Gould Instrument Co., Cleveland, OH). This catheter was then exchanged for a polyethylene catheter.

Using techniques previously described, mean circulatory filling pressure, venous compliance, and blood volume were measured.[12] In brief, transient circulatory arrest was produced by inflation of a balloon in the right atrium. Mean circulatory filling pressure was calculated from the venous and arterial plateau pressures. This procedure was repeated after ±10% changes in blood volume. Venous compliance was calculated from the slope of the total vascular pressure–volume relation.

Pressure–volume data from the isolated left ventricle were recorded using methods previously described.[8,15] These measurements were made in the excised left ventricle with a timed infusion of normal saline.

**Isometric muscle function:** Rats were killed by decapitation, the heart rapidly excised, and the noninfarcted posterior papillary muscle was dissected free.[14] The muscle was suspended vertically from an isometric force transducer (Metrigram Mtm, Gould Instrument Co.) and isometric function and passive myocardial stiffness were measured.[14]

**Histologic studies:** After the papillary muscle was removed, the heart was separated into right ventricle and left ventricle plus septum, weighed, and immersion-fixed in 10% buffered formalin. Thin sections of the ventricle were stained with Masson's trichrome and infarct size was measured by tracing the outline of the infarcted and noninfarcted regions of the ventricle at 4 different levels. Infarct size is reported as the mean percent of epicardial and endocardial circumference occupied by scar tissue for the 4 sections.

Papillary muscles were processed as noted above and cross-sectional slices were made at 3 different levels. Cross-sectional areas of approximately 100 myocytes were measured for each papillary muscle.[14] The operator was blinded to the experimental group during the analysis.

Myocardial hydroxyproline content was measured using previously described methods.[14] Briefly, the scar was removed from the left ventricle and the tissue was frozen. At a later time, the tissue was dried, weighed, and hydrolyzed in 6 N HCl at 105°C. Hydroxyproline content of the samples was determined using spectrophotometry at 557 nm.

**Statistical analysis:** Values are reported as mean ± standard error of the mean. Muscle stiffness constants, regression coefficients, and values for venous compliance were determined by linear regression using the method of least squares. Isometric parameters are means of 3–5 twitches and muscle stiffness values are the mean of at least 3 stretches for each muscle. Differences between groups were detected with 1-way analysis of variance and intergroup comparisons were performed using the Student-Newman-Keuls test or Dunnett's test for multiple comparisons against a single control.

## RESULTS

**Hemodynamic studies:** The baseline chamber weights, heart weights and hemodynamics are shown in Figure 1. The rats with heart failure after myocardial infarction had increased right ventricular (RV) weights, increased RV/body weight, but no change in LV weight/body weight. In the captopril-treated rats body weight was unchanged while LV weight, RV weight, and RV/body weight were all decreased compared with untreated rats with large infarctions.

The hemodynamic changes are shown in Figure 2. In the rats with heart failure there was no change in heart rate, a decrease in mean aortic pressure and an increase in LV end-diastolic and right atrial pressures. Hematocrit was unchanged, mean circu-

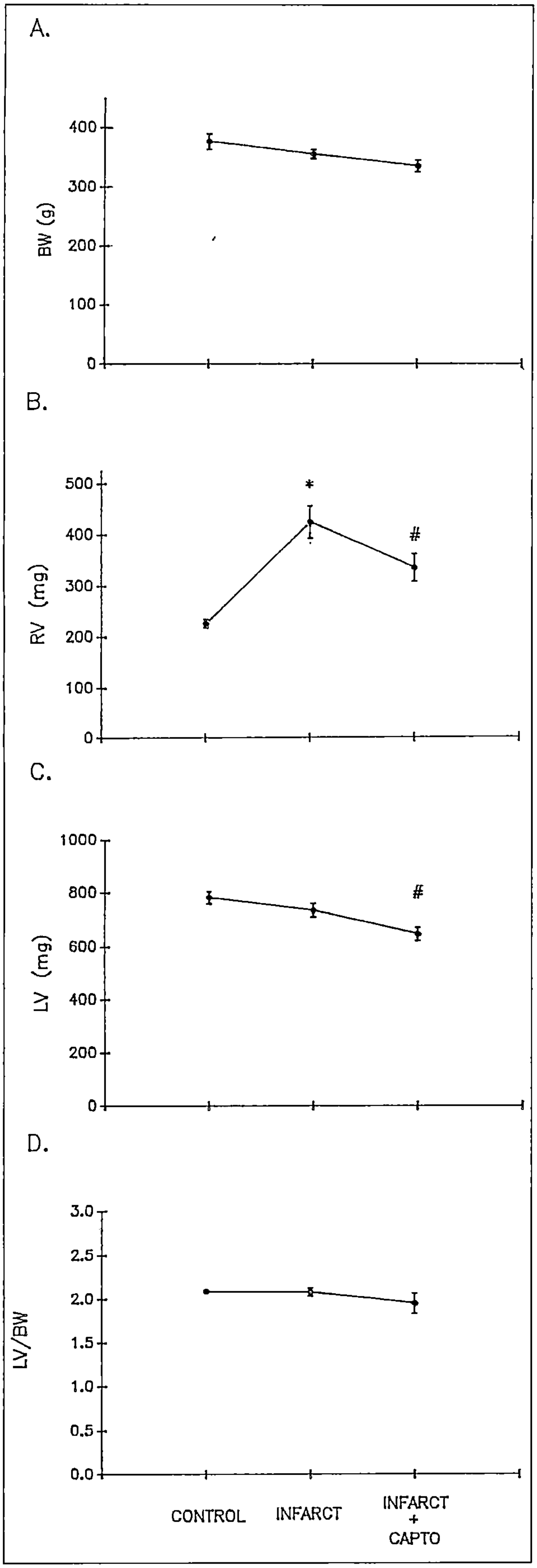


**FIGURE 1. Changes in body weight (BW) *(A)*, right ventricular (RV) weight *(B)*, left ventricular (LV) weight *(C)* and left ventricular weight/body weight *(D)*. Values are mean ± standard error of the mean. *p $<0.05$, control versus infarct (n = 11); #p $<0.05$ infarct versus infarct-captopril (CAPTO) (n = 9). Note that comparisons were not made between control versus infarct-captopril.**

latory filling pressure and blood volume were increased, and venous compliance was decreased in the rats with heart failure compared to control (Figure 3). Treatment of rats with heart failure with captopril did not change heart rate, further decreased mean aortic pressure and LV end-diastolic pressure (Figure 2). In the captopril-treated rats with large infarctions, hematocrit was unchanged, mean circulatory filling pressure and blood volume decreased, and venous compliance increased. The end result of these hemodynamic changes was that in the rats with heart failure, the passive LV pressure–volume relation was shifted away from the pressure axis, indicating LV dilation. Captopril treatment in the infarct rats did not shift the pressure–volume curve but did decrease operating LV end-diastolic pressure and volume.[8]

**Papillary muscle studies:** In 11 rats with large infarctions and heart failure, there were no changes in papillary muscle weight (7.4 ± 0.6 mg vs 6.9 ± 0.7 mg) or muscle cross-sectional area (1.2 ± 0.1 $mm^2$ vs 1.0 ± 0.1 $mm^2$), but there was a decrease ($p < 0.05$) in the length associated with maximum developed tension (5.6 ± 0.4 mm vs 7.1 ± 0.4 mm). Myocyte cross-sectional area was increased (Figure 4) and collagen content, defined by changes in hydroxproline levels in the noninfarcted myocardium, was increased (8.5 ± 0.9 μg/mg dry weight vs 3.3 ± 0.3 μg/mg dry weight; $p < 0.05$). There were also decreases in developed tension and peak rate of tension increase, a prolongation of time to peak tension, and an increase in muscle stiffness (Figure 4). With captopril treatment in 9 rats with large infarctions, the morphologic changes returned to baseline, i.e., myocyte cross-sectional area (567 ± 41 $\mu m^2$) was not different than control rats. Hydroxyproline content remained increased (7.2 ± 0.2 μg/mg dry weight, n = 3). With captopril treatment, developed tension, the peak rate of tension development, and the muscle stiffness constant remained abnormal. The only mechanical benefit that resulted from captopril treatment was a shortening of the prolongation of the time to peak tension (Figure 4).

## DISCUSSION

After coronary artery ligation that results in large infarction, rats develop chronic congestive

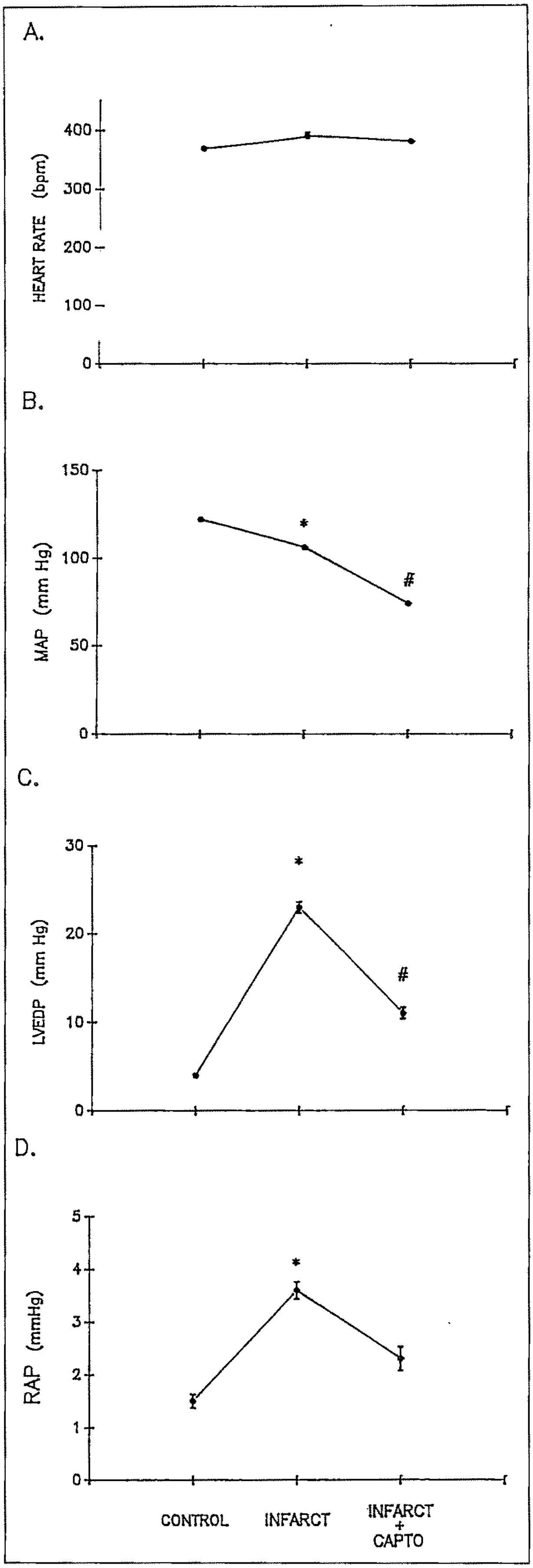
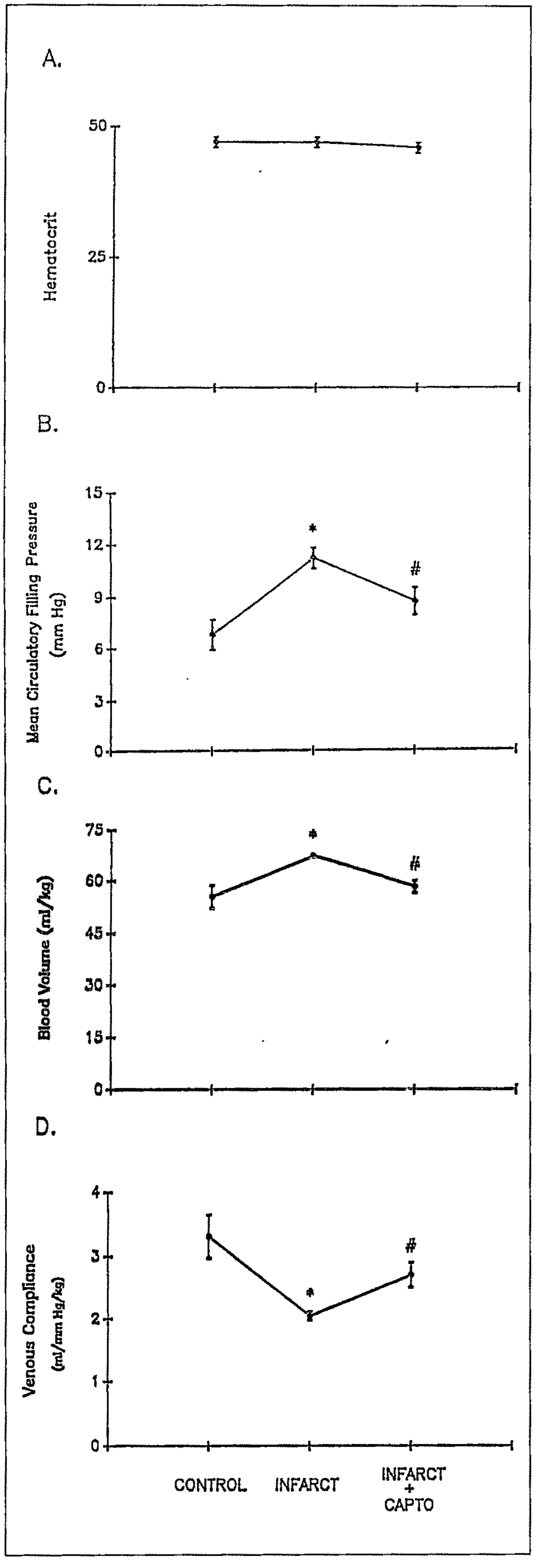


**FIGURE 2. A, changes in heart rate; B, mean aortic pressure (MAP), C, left ventricular end-diastolic pressure (LVEDP) and D, right atrial pressure (RAP). Values are mean ± standard error of the mean. *p <0.05, control versus infarct (n = 9); #p <0.05 infarct versus infarct-captopril (CAPTO) (n = 8). Note that comparisons were not made between control versus infarct-captopril.**



heart failure. These rats show hemodynamic changes similar to those seen in humans with ischemic LV dysfunction, making this a useful model to study the pathophysiology of heart failure after myocardial infarction. When examined at the organ level, there is compromised LV function with alterations in systolic and diastolic function. The important changes that we found in our studies were increased LV end-diastolic pressure and volume, a prolongation of LV relaxation, and decreases in ejection fraction and stressed cardiac output.[8,9,15] The peripheral circulatory changes that accompany these cardiac abnormalities are decreases in venous compliance and increases in total blood volume.[8,12] At the muscle level, the noninfarcted myocardium hypertrophies and, in the process, collagen content and passive stiffness are increased, the ability to develop tension is decreased, and time to peak tension is prolonged.

Treatment of heart failure with captopril is thought to be primarily directed at the peripheral circulation. Captopril dilates both the arterial and venous circulations. In addition, at least in the rat model, captopril treatment decreases blood volume. This results in a decrease in LV end-diastolic pressure and volume. Despite the benefit on hemodynamics, this improvement in loading conditions results in only a modest improvement in muscle function, i.e., there are no changes in developed tension or passive stiffness. Time to peak tension is the only parameter of isometric function that was improved during captopril treatment.

In ischemic LV dysfunction, failure of the heart at the organ level may be due to marked increases in afterload, loss of contractile units, or dysfunction of individual contractile units. The loss of functioning myocardium is an irreversible process; however, abnormalities of ventricular loading conditions and dysfunction of surviving myocardium may potentially be prevented or improved by appropriate treatment. The results of our study illustrate the necessity to distinguish between abnormalities of ventricular loading conditions and impaired myocardial function when examining therapies for heart failure. These investigations can only be carried out in animal models like the rat where structure and function studies can be done at both

**FIGURE 3. Changes in hematocrit *(A)*, mean circulatory filling pressure *(B)*, blood volume *(C)* and venous compliance *(D)*. Values are mean ± standard error of the mean. *p $< 0.05$, control versus infarct (n = 11); #p $< 0.05$ infarct versus infarct-captopril (CAPTO) (n = 9). Note that comparisons were not made between control versus infarct-captopril.**

the organ and muscle level. Our original hypothesis was that ventricular unloading with captopril would improve organ function and this, in turn, would result in improved muscle function. We were somewhat surprised with our results.

**Structural changes:** An important structural change that occurred in the heart as a result of captopril treatment in rats with large infarctions was that RV weight returned toward normal. LV weight also decreased with captopril. An increase in RV weight is a consistent finding in this model of heart failure.[5,8,16] Presumably, this RV hypertrophy is a response to the increased afterload, i.e., passive pulmonary hypertension resulting from increases in LV end-diastolic pressure. The decrease in RV weight in captopril-treated heart failure rats is most likely due to a decrease in RV afterload, which is a consequence of a lower LV end-diastolic pressure. After large myocardial infarction in the rat, LV weight does not change because the surviving myocardium hypertrophies enough to make up for the myocardium that was replaced by scar tissue. Captopril lowers LV weight in both infarct and normal rats. This effect could be attributed to the lowering of arterial pressure and/or to a loss of the tropic effects of angiotensin II. Changes in myocyte cross-sectional area parallel those of chamber weight during captopril treatment in control and infarct rats.

The development of myocyte hypertrophy in the noninfarcted myocardium may be due to increases in both preload and afterload, as well to the trophic effects of angiotensin II. Previous studies have shown that myocyte length and diameter are increased in noninfarcted myocardium.[17,18] This pattern of morphologic change is consistent with a combination of increased diastolic and systolic wall stress. Our data show that captopril caused a reduction in myocyte cross-sectional area, probably because of its afterload-reducing effects. Although we did not measure myocyte length, this may have also decreased due to the preload reduction seen with captopril.

The changes in collagen content are interesting. It has been postulated that alterations in collagen content and type are responsible for some of the

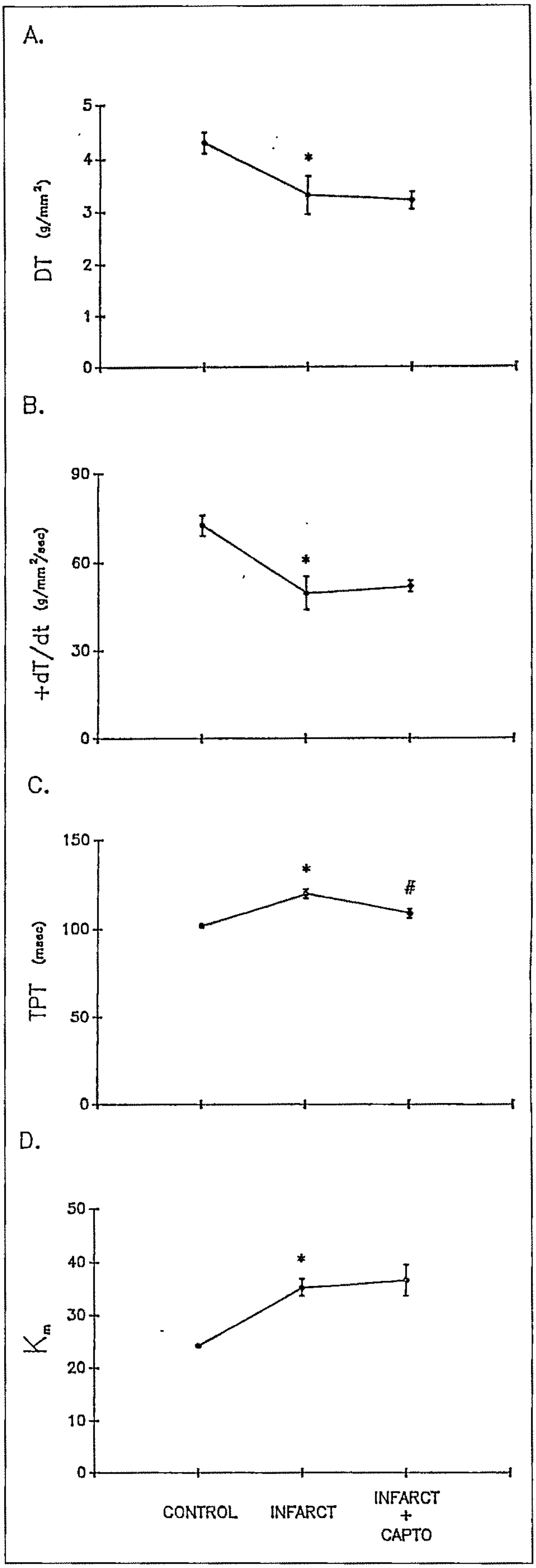


**FIGURE 4. Changes in developed tension *(A)*, the first derivative of developed tension (DT) with respect to time *(B)*, the time to peak tension *(C)* and the muscle stiffness constant *(D)*. Values are mean ± standard error of the mean. $dT/dt$ = peak rate of tension increase ($g/mm^2/s$); $K_m$ = muscle stiffness constant; TPT = time to peak tension (ms); *$p < 0.05$, control versus infarct; #$p < 0.05$ infarct versus infarct-captopril (CAPTO). Note that comparisons were not made between control versus infarct-captopril.**

functional changes that occur in the hypertrophied myocardium, particularly with respect to the passive-elastic properties of the tissue.[19,20] Since angiotensin II is a trophic hormone, it is possible that increased levels of angiotensin II could result in increased fibroblast growth and proliferation. Recent studies have suggested that only myocardial hypertrophy that is accompanied by activation of the renin-angiotensin system shows increased interstitial fibrosis.[21] One problem with both of these potential explanations is that, in our study, captopril changed loading conditions and presumably decreased angiotensin II levels but this did not result in decreases in fibrosis, at least as measured by hydroxyproline content.

**Functional changes:** The functional studies in the papillary muscles showed that there was a decrease in contractility. We anticipated that the combination of pressure and volume overload that occurs in this model would result in compromised muscle function. In the only other report of changes in papillary muscle function after coronary artery ligation in rats, Bing et al[22] reported findings that were similar to ours, i.e., prolonged time to peak force development at 3 weeks after infarction. However, they found no difference in developed force or peak rate of force development. Their results, in conjunction with the 6-week data presented here, suggest that heart failure after infarction presents as a continuum of compromised muscle function with maintenance of muscle function initially but deterioration over time. In this context, it is important that we consider the possibility that the beneficial response to captopril may also be time dependent, and longer term treatment could result in more improvement in muscle function.

One possible explanation for the changes in muscle function summarized above is an alteration in myosin isoform expression. In the rat the fast activity myosin isoform, $V_1$, predominates. With the development of heart failure, the amount of $V_1$ decreases and the amount of the slower activity isoform, $V_3$, increases.[13] Although these changes in myosin isoform expression may be in part responsible for the changes in muscle function in our study, similar decreases in muscle function have occurred in other animal models of hypertrophy and failure in which the isoform composition is predominantly $V_3$, although this down-regulation occurs much later in the development of disease.[4] In addition, heart failure develops in patients after large myocardial infarctions and the human ventricle is essentially all $V_3$. Thus, the change in myosin isoform expression is not the entire explanation. Interestingly, there is one report showing that captopril causes a modest increase in the $V_1$ isoform in the rat infarct model of heart failure.[23] This shift to the myosin isoform with the faster activity could explain the improvement of the prolonged time to peak tension that was seen with captopril treatment in the rats with heart failure.

Although any alteration in inotropic state is ultimately biochemically mediated, the changes in contractile function that occur at the muscle level in this model may represent the biochemical responses to increases in load. After myocardial infarction, there is a decrease in stroke volume that results in peripheral vasoconstriction and compensatory LV dilation with increases in preload and afterload. These effects are additive and increase myocardial stress, which is an important stimulus of myocardial hypertrophy. Mann et al[24] have shown that isolated myocytes from pressure-overloaded hearts demonstrate mechanical dysfunction, indicating myocyte abnormalities that may be independent of changes in myocardial blood flow or extracellular matrix. It is possible that persistent contractile dysfunction at the cellular level is a universal, time-dependent response to chronic increases in load. It is not clear whether in the rat infarct model contractile dysfunction could be reversed by longer duration of treatment with captopril.

**Peripheral circulation:** The beneficial effects of captopril on the peripheral circulation are important. The combination of arterial and venous dilation that occur with ACE inhibition may be uniquely suited to the treatment of the combined pressure and volume overload state that occurs in heart failure. For example, previous work from our laboratory showed that when rats with heart failure were treated with hydralazine, an arterial vasodilator, arterial pressure decreased to a similar extent as in captopril-treated rats, but there were no changes in LV end-diastolic pressure or volume.[8] We believe that this was because hydralazine had no effect on the venous circulation, i.e., venous compliance did not change and there was no change in blood volume. Thus, in the rat model, it appears that specific peripheral circulatory changes are necessary to produce ventricular remodeling, the most important of which are a decrease in afterload coupled with decreases in total blood volume and increases in venous compliance.

**Conclusions:** The study of the pathophysiology of heart failure and its treatment at both the organ and muscle level has increased our understanding of the sequence of events that occur when heart failure develops. It is possible that adverse ventricular remodeling is the basis of progressive LV dysfunction. In this analysis, heart failure could be defined as a mechanical problem. Following large myocardial infarction and compensatory dilation, the noninfarcted myocardium undergoes hypertrophy as a consequence of increased wall stress. This tends to reduce wall stress toward normal. However, wall stress remains elevated due to incomplete compensatory hypertrophy. These alterations in load at the organ level lead to persistence of mechanical dysfunction at the cellular and muscle level. Treatment with captopril results in beneficial effects in the peripheral circulation where the combination of arterial and venous dilation lowers preload and afterload. However, although this would tend to lower wall stress and thus decrease the mechanical forces applied to the cell, myocyte and ventricular hypertrophy would be also reduced both by the partial removal of the mechanical stimulus and the inhibition of the direct trophic effects of angiotensin II. The beneficial effect of compensatory hypertrophy on wall and myocyte stress would thus be blunted. This might explain the inability of captopril to restore muscle function to normal. Further investigations, which should include accurate measurement of regional wall stress, will be required to verify some of these speculations.

Lastly, it is important to address the question, "Are the beneficial effects of ACE inhibitors due solely to reduction of angiotensin II levels?" Support for this argument comes from work done in our laboratory that showed that administration of a new specific nonpeptide angiotensin II-blocking agent, DuP 753, resulted in the same hemodynamic changes as those produced by captopril in the rat infarct model of heart failure.[9] It is also important to consider the possibility that a combination of direct-acting arterial and venous dilating agents would have similar effects. Preliminary data from the Veterans Administration Cooperative Trial (VHEFT II), which is comparing the effects of ACE inhibition with a combination of isosorbide dinitrate and hydralazine on patients with heart failure, suggest that patients treated with ACE inhibition had improved survival.[3] As further data accrue, the mechanisms that may contribute to the particular effectiveness of converting enzyme inhibitors in the treatment of heart failure should become more clear.

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# Myocardial Infarct Expansion: Recognition, Significance and Pathology

James L. Weiss, MD, Paolo N. Marino, MD, and Edward P. Shapiro, MD

**Infarct expansion can be defined pathologically as a distortion of ventricular topography produced by thinning and disproportionate dilation of the infarct segment. Large transmural infarcts tend to be associated with greater propensity for infarct expansion. Two-dimensional echocardiography has made it feasible to detect these acute alterations in cardiac topography by serial examination of patients with acute myocardial infarction. A practical approach to the echocardiographic quantification of expansion involves analysis of end-diastolic cross-sectional echo views at the papillary muscle level, which can be used as fixed internal landmarks to divide the left ventricle into 2 segments, anterior and posterior. An off-line computer system can be used to track relative lengths of these segments as well as their thicknesses over time. In the initial clinical study, one third of patients with acute anterior transmural infarcts showed an average 50% increase in the infarct segment length beginning within the first 3 days of infarction, characterized by disproportionate progressive dilation and transmural thinning of this zone. These patients demonstrated a significantly higher mortality than those without expansion. Later studies demonstrated not only continuing dilation of the infarcted anterior wall, but also progressive dilation of the noninfarcted posterior wall, underscoring the importance of continuing long-term noninvasive follow-up. Not only is expansion associated with a poor clinical outcome; it has also been shown experimentally and clinically to be modifiable or even preventable by various therapeutic maneuvers, which may well improve survival. Because of the limitations of the echocardiographic window, it is often possible to obtain only a single cross-sectional view of high quality, and even then technical quality may not be sufficiently high to enable detailed quantitative analysis. Newer technologies appear to have overcome many of these problems. Magnetic resonance imaging (MRI) acquires data in a spatially unambiguous fashion so that the 3-dimensional relationships of one image plane to another are easily ascertained. Moreover, there are fewer technical restrictions on the acquisition of high quality images. A new MRI method has been developed to improve quantification of regional ventricular function and topography. Myocardial tissue tagging, in essence an electronic MR marker applied to the myocardium that persists through ejection, enables one to track specific regions of myocardium through the cardiac cycle. This approach appears to quantify wall topography and thickness with a higher degree of accuracy than previously possible noninvasively and should enable more accurate evaluation of both natural history and therapeutic strategies by more precisely quantifying ventricular remodeling in patients with myocardial infarction.**

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Myocardial infarct expansion may be defined pathologically as a distortion of the ventricular topography produced by thinning and disproportionate dilation of the infarcted segment, which causes an increase in the proportion of surface area of the left ventricle occupied by necrotic myocardium. This phenomenon, which does not result from new myocardial necrosis, should be distinguished clearly from infarct extension, a process that appears to be the result of additional, new injury. Infarct expansion generally occurs within the first 24 hours after myocardial infarction, and infarct extension generally occurs at a later time. Large transmural infarcts, mainly anterior, characterize most patients with marked infarct expansion. Larger infarcts tend to be associated with greater propensity for infarct expansion.

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## RECOGNITION

In its capacity for repeated noninvasive examination, echocardiography, over the past decade, raised the possibility of serial evaluation of left ventricular size and topography in acute myocardial infarction. The initial impetus for using echocardiography in this way was provided by pathologic studies. Postmortem studies of patients dying within 30 days of acute transmural myocardial infarction had shown that up to two thirds of such patients had some thinning and dilation of the infarcted region within 1 week of infarction,[1] and that in approximately one third of hearts with transmural infarcts there was marked expansion of the infarcted zone, resulting in obvious cardiac dilation. This process occurred with little or no histologic evidence of infarct extension or further necrosis after the initial acute event.

The advent of 2-dimensional echocardiography made it feasible to detect such acute alterations in cardiac topography by serial examination of patients with acute myocardial infarction and to make the antemortem diagnosis noninvasively.[2] Quantitative evaluation of serial echocardiograms was accomplished by a computer-aided system for contouring myocardial borders and quantifying regional wall thickness and segment lengths.[3] This type of analysis could not be achieved by subjective visual impression. Using a short-axis echocardiographic view at the level of the papillary muscles, regional segment lengths and wall thicknesses were calculated. In the initial clinical study,[2] 28 patients with acute anterior transmural myocardial infarction were identified. One third of patients with anterior transmural infarction showed infarct expansion during the first few days after admission, characterized by disproportionate dilation (approximately 48% increase) and transmural thinning of the infarcted zone, accompanied by an increase in total left ventricular circumference (approximately 25%).

Myocardial infarct expansion was considered clinically important because, although patients with regional expansion did not have a significantly higher peak creatine kinase or Killip classification than those without expansion, they did have a significantly greater 8-week mortality (4 of 8 vs 0 of 20). Thus, a selective topographic change in myocardial structure within the area of necrotic myocardium was responsible for a major alteration in left ventricular topography. The mortality data suggested functional and possibly prognostic implications. If patients in whom regional infarct dilation or infarct expansion develops could be identified early by sequential echocardiography, it was considered likely that conventional management of myocardial infarction could be altered in favor of closer and more prolonged monitoring. Echocardiography, therefore, has a definite and useful role in the clinical evaluation of patients with acute myocardial infarction. It provides both immediate and serial assessment of regional and global ventricular function and topography.

As pointed out in the initial echocardiographic study of this entity, expansion appears as a clinically silent process initially, without specific symptoms in most patients. Yet, the greater extent of functional deterioration that characterizes these patients, possibly related to increases in wall stress imposed by infarct thinning and dilation on the noninfarcted myocardium, together with a significantly higher mortality,[2] justifies efforts for early recognition of this complication. Two-dimensional echocardiography is an excellent technique for detecting developing alterations in cardiac topography by serial examination of acutely infarcted patients. This technique has been used in numerous subsequent studies to examine both the acute and chronic sequelae of infarct expansion.

## SIGNIFICANCE

Early clinical studies have shown that overall cardiac enlargement is associated with an adverse prognosis.[4–7] The initial echocardiographic study had indicated that cardiac enlargement after myocardial infarction was likewise associated with increased mortality.[2] The mechanism of early dilation of the left ventricle in myocardial infarction, however, had not been well defined. Such early dilation may be due to the Frank–Starling effect, which results in an increase in the length of the uninfarcted segments in response to a reduction in contractile muscle mass. In contrast to this adaptive physiologic mechanism, left ventricular dilation may alternatively be caused by a pathologic process that stretches and thins the infarcted myocardial segment, i.e., infarct expansion.

To determine the relative contributions of these 2 mechanisms to left ventricular dilation after initial anterior transmural infarction, Erlebacher and colleagues[8] obtained 2-dimensional echocardiograms from 27 patients within 72 hours of the onset of symptoms of myocardial infarction and from 13 healthy control subjects. A minor axis echocardiographic view at the papillary muscle level was used, as before, to delineate anterior and posterior endocardial segment lengths at end-diastole, which were measured with a off-line computer system. Papillary muscles demarcated the anterior and posterior segments. Anterior infarcted segment lengths were compared to age- and sex-matched control subjects, as were posterior, uninfarcted segment lengths.

Anterior infarcted segment lengths in patients with myocardial infarction averaged 11.6 cm, whereas in control subjects anterior segment length averaged 8.6 cm ($p < 0.001$). Posterior, uninfarcted segment lengths in patients were not significantly different from posterior segment lengths in the normal control subjects, both averaging approximately 5.4 cm. Therefore, measurable left ventricular dilation during the first 3 days (and in 8 cases <24 hours) after transmural infarction appears to be due to selective dilation of the infarcted segment, but not of the normal noninfarcted segment. Viable uninfarcted myocardial segments did not, in this early postinfarction period, appear to participate significantly in the acute ventricular enlargement. Infarct expansion thus appears to be the major cause of early left ventricular dilation in these patients. By increasing the size of the left ventricle, infarct expansion causes an additional load to be placed on the remaining, functioning myocardium. Thus, infarcts of similar size with or without expansion may have differing effects on ventricular mechanics and clinical outcome.

In these patients, preexisting hypertension appeared to play a role in the genesis of infarct expansion. There was a significantly higher prevalence of a history of hypertension (>140/90 mm Hg) in patients who developed infarct expansion than in those who did not (10 of 16 in the expansion group, 2 of 11 in the nonexpansion group). However, the frequency of hypertension on admission to the hospital did not differ between the 2 groups. A history of hypertension frequently predates left ventricular aneurysm formation, as disclosed at postmortem examination.[9,10] Insofar as infarct expansion occurs early, one might suggest that general cardiac enlargement and/or discrete ventricular aneurysm formation are apt to be determined in the first days or hours following infarction.

This study also supported previous reports in which cardiomegaly, as measured radiographically,[4–7] confers a poor prognosis. This includes New York Heart Association (NYHA) functional deterioration. Despite similar infarct sizes as estimated by peak serum creatine kinase levels, patients with infarct expansion had significantly more exercise intolerance related to angina and dyspnea than those without expansion. There was also a nonsignificant trend toward higher hospital mortality in patients with infarct expansion. Likewise, 1-year mortality showed a higher, nonsignificant trend in the expansion versus the nonexpansion group. These observations suggested that infarct expansion, even in the early hours of infarction, confers a poor prognosis.

Another consequence of infarct expansion is an increase in the surface extent of infarcted myocardium without any increase in infarcted mass. This bears importantly on methods of infarct size estimation that depend on measurement of surface area of ventricular dysfunction or scintigraphic defect size. In the presence of infarct expansion, any method that measures the area but not the mass of abnormal myocardium is likely to overestimate true infarct size.

Echocardiography has been used to assess not only the early sequelae but also the later effects of acute infarct dilation on heart size. Dilation of the infarct zone has been shown to cause regional left ventricular dilation within hours to days of transmural anterior infarction. In a subsequent study, serial echocardiographic studies were obtained in 13 patients with acute anterior transmural infarction over a mean period of 13 months after the acute event (3–30 months).[11] Echocardiograms were taken beginning 10–21 days after anterior transmural infarction. Using methods to ensure consistency of echocardiographic views in the serial examinations, measurements of ventricular dimensions were obtained from short-axis views at the papillary muscle tips, which divided the ventricle into anterior and posterior segment lengths. Anterior and posterior segmental dilation in each patient was assessed from the slope of a regression line of segment length versus time. Patients were classified into those with and without infarct expansion. Expansion was defined as an anterior segment length 10–21 days after infarction that exceeded the upper limits of normal determined from 13 age- and sex-matched normal control subjects. At 10–21 days after infarction, the average anterior segment length in the 7 patients with expansion was 65% greater than in normal control subjects. Seven patients with expansion showed significant and continuing dilation during the long-term observation of both the infarcted anterior and uninfarcted posterior segments. The average increase in the anterior segment length was 1.1 cm (8%) and in posterior segment length, 0.9 cm (19%). This represents an average increase in overall left ventricular circumference of 11% during the observation period. The 6 patients without infarct expansion showed no significant change in anterior or posterior segment length. Six of the 7 patients with infarct expansion were functionally limited by dyspnea and angina, or both; no patient without infarct expansion had functional cardiac limitation.

McKay et al[12] similarly demonstrated with contrast ventriculography the presence of ventricular enlargement 2 weeks after transmural myocardial infarction. Echocardiographic studies suggested that this dilation involved both the infarcted and noninfarcted ventricular segments. The extent of akinesis and dyskinesis present on the early ventriculogram appeared to correlate closely with the magnitude of total left ventricular cavity enlargement.

It would appear, therefore, that infarct expansion occurring within 3 weeks of transmural myocardial infarction is the main contributor to left ventricular dilation and is associated with impaired functional status. Moreover, a significant increase in ventricular size due to infarct expansion appears to predict later chronic, progressive ventricular enlargement due to lengthening of both the infarcted zone and the uninfarcted segment. Ventricular dilation after acute anterior myocardial infarction thus begets continued dilation. Regional infarct expansion, which usually occurs soon after myocardial infarction, leads to further progressive dilation of the ventricle as a whole during long-term observation. Therefore, once a certain heart size is reached, the tendency to further dilation of both the infarcted and uninfarcted segments is established.

The above studies support the conclusion that in a large proportion of patients with anterior acute transmural infarction studied early after the acute event, echocardiography can identify disproportionate dilation of the infarcted zone that appears to be associated with an adverse prognosis, both in terms of functional status and mortality. The process continues, although to a lesser extent, during the subsequent 3 months and is associated with impaired functional status.

## PATHOLOGIC MECHANISMS OF INFARCT EXPANSION

The precise mechanism of infarct expansion has been the subject of intense animal investigation. Studies performed in dog and rat models[13,14] suggested that 2 conditions are necessary to produce infarct expansion: transmurality and a threshold mass of infarcted myocardium. These observations may explain why expansion is generally seen clinically in the setting of a large anterior transmural infarction,[2] although the direct relation between the degree of expansion and infarct size has been questioned.[15]

Several hypotheses have been put forth to define the pathophysiology of expansion. In a recent study on the cellular mechanisms of infarct expansion, Weisman and colleagues[16] suggested at least 5 kinds of cellular changes that could explain such gross alterations in cardiac topography. These include: (1) myocyte hypertrophy as a means of producing myocyte elongation and chamber enlargement; (2) necrosis of myocytes, contributing to wall thinning and dilation; (3) a reduction in intracellular space, which could result in wall thinning; (4) individual myocyte stretch, resulting in cell lengthening and thinning; and (5) rearrangement of myocyte bundles, with the result that fewer cells make up the thickness across the ventricular wall, with the total number of cells per unit length unchanged.[16] In rat hearts, wall thinning occurred in all regions but was most pronounced in the infarct zone. A decrease in the number of cells across the wall accompanied the wall thinning at each site, and this change correlated strongly with change in wall thickness. Only within the infarct zone did cell density increase from controls and accounted for only 20% of the thinning in that region. This change in density was attributable to both cell stretch and decrease in the intracellular space. In humans, a similar strong correlation between wall thinning and decreased number of cells across the wall was identified. Thus, a decrease in the number of myocytes across the wall accounts for most wall thinning in the infarct zone, as seen in myocardial infarct expansion, and for all the thinning of noninfarcted regions in both rat and human models of myocardial infarct expansion. Cell stretch or decrease in intracellular space between myocytes occurs only within the infarct region and contributes to infarct thinning to a considerably lesser extent.

## NEWER METHODS OF IDENTIFYING AND QUANTIFYING INFARCT EXPANSION: MAGNETIC RESONANCE IMAGING

The use of echocardiography has elucidated a heretofore unrecognized early complication of acute myocardial infarction, infarct expansion. Echocardiography in the assessment of acute and chronic changes in cardiac architecture is not without its limitations. Because of limitations in the echocardiographic window, it is often possible to obtain only a single cross-sectional view of high quality, and even then technical quality may not be sufficiently uniform or high to enable the computer-assisted quantitative analysis that is so necessary for the accurate assessment of infarct expansion. Furthermore, the 3-dimensional interrelations of one image plane to another may be difficult to ascertain. Newer technologies appear to have overcome many of these problems. Magnetic resonance imaging (MRI) is one such technology. MRI acquires data in a spatially unambiguous fashion so that the 3-dimensional interrelations of one image plane to another are easily ascertained. Moreover, in most cases there are far fewer technical restrictions on the acquisition of high quality images. The multiplanar nature of MR image acquisition, in any plane desired, is a feature that is unique to this imaging modality. Therefore, MRI appears well suited to the highly accurate quantification of both global and regional left ventricular function and architecture. One limitation of the measurement of wall thickness or wall thickening by echocardiography or other planar imaging techniques is the oblique course of the plane of the cross-sectional image through the LV wall, particularly near the apex. This obliquity results in overestimation of wall thickness by "in plane" analysis methods. Further, any change in the tilt of the LV wall with regard to the image plane between end-diastole and end-systole will affect the accuracy of thickening and thickness measurements considerably.

To overcome these limitations, we have developed a method to quantify and map regional wall thickening throughout the left ventricle with MRI.[17] In contrast to those methods that measure planar wall thickness, this method uses the 3-dimensional geometry of the LV to calculate true or perpendicular thickness of the wall. A schematic representation of a 3-dimensional volume element between 2 imaging planes is shown in Figure 1. With this technique, the average perpendicular thickness may be computed from any 2 adjacent planar images. Although the problem of image obliquity is amplified toward the apex and may not be apparent at the midventricular level for the normal heart, it may nonetheless introduce significant error if the image plane is not strictly perpendicular to the wall or if the heart is distorted by a disease process such as a transmural infarct, infarct expansion, or ventricular aneurysm. Therefore, a method of measuring thickness that is independent of the angle between the image plane and the LV wall should enhance significantly the accuracy of measurements of wall thickness and topography. This 3-dimensional volume element approach has been shown to result in significantly less variability of normal wall thickening, and in better discrimination of the ischemic from nonischemic zones in an animal model of acute ischemia.[17]

A second MRI method has been developed to improve quantification of regional ventricular function and topography. Myocardial tissue tagging is a new MRI technique, and unavailable with other imaging modalities.[18] Tagging labels specific regions of myocardium just prior to image acquisition. Figure 2 shows two images of the heart in an anesthetized dog (1.5 Tesla GE scanner). These cross-sectional images show 8 equidistant tags emanating from the left ventricular cavity. Myocardial tags traverse the heart and surrounding fixed structures, which serve as stable references to enable tracking of the heart itself. It was hypothesized that tags could be used to quantify rigid body motion, deformation, and torsion noninvasively, and that further, such quantification would significantly improve measures of regional function without contamination by different segments of the myocardium throughout the cardiac cycle. Rather, one would be comparing identical segments. Tagging is achieved by selective radiofrequency saturation of the thin planes intersecting the myocardium perpendicular to the cross-sectional images (Figure 2). In the tagged regions, protons are in a different state of magnetization from surrounding tissues. This produces a contrasting signal that appears as a contrasting stripe embedded or inscribed in the myocardium and surrounding stationary structures. Applied at end-diastole, tags persist for up to 500 msec, thus enabling tracking of tags throughout ejection. It is thus possible to track any intervening displacement or deformation of the tag lines as the change in the tag position or shape relative to its end-diastolic position. One can thus

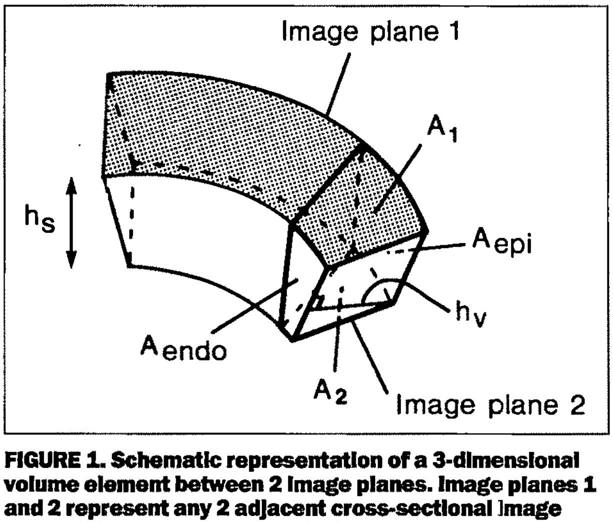
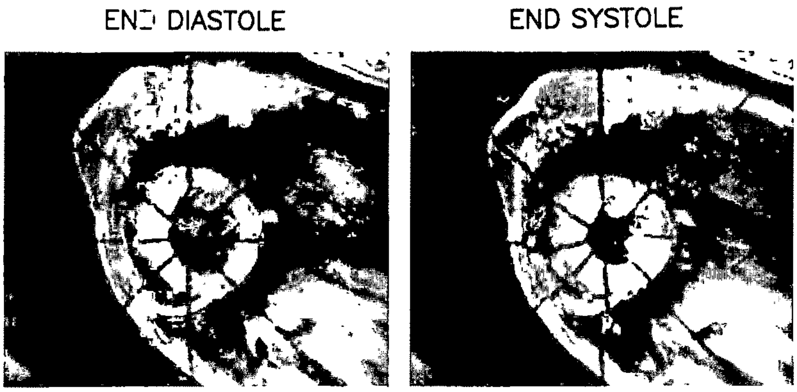


**FIGURE 1. Schematic representation of a 3-dimensional volume element between 2 image planes. Image planes 1 and 2 represent any 2 adjacent cross-sectional image planes. The average perpendicular thickness ($h_v$) is computed by dividing its volume by the mean of the endocardial and epicardial areas ($A_{endo}$, $A_{epi}$). $h_s$ = distance between imaging planes. Actual calculations of endocardial and epicardial segment lengths are based on linear approximations of curved edges. $A_1$ and $A_2$, areas of the top and bottom of the volume element, respectively. (Reprinted with permission from *Circulation*.[17])**



END DIASTOLE END SYSTOLE

**FIGURE 2. End-diastolic and end-systolic magnetic resonance images, cross-sectional views (GE Signa scanner, 1.5T). Mid-left ventricular views, showing 8 equidistant tags (dark stripes) emanating from the left ventricular cavity. The tags traverse the heart and the surrounding fixed structures in this anesthetized dog, which serve as a stable reference to enable tracking of the heart itself. The myocardial tags, appearing as contrasting stripes, are actually embedded or inscribed in the myocardium and surrounding stationary structures. Tagging in this example shows counterclockwise rotation when comparing the end-systolic position of the myocardial tags, particularly in the inferoseptal region, to the position of the corresponding tag lines as they traverse fixed extracardiac structures.**

compare where the tags *were* at end-diastole to where they *are* at end-systole. As seen in Figure 2, nonuniform counterclockwise rotation of a cross-sectional slice of myocardium is evident. Regional counterclockwise rotation is seen when comparing the end-diastolic position of the myocardial tags in the inferoseptal region to the position of the corresponding tags as they traverse the fixed noncardiac structures.

Using myocardial tags, we have shown that quantification of regional myocardial function and architecture will be improved by tagging without contamination by different segments of the moving myocardium throughout the cardiac cycle.[19]

With the combination of a 3-dimensional volume element approach to improve the accuracy of quantifying wall thickness and thickening, and magnetic resonance tissue tagging to track the motion of specific regions of the myocardium through the cardiac cycle, we feel we now have a considerably more accurate means of detecting and quantifying infarct expansion in patients. Furthermore, MRI makes it possible to quantify changes in left ventricular architecture throughout the entire left ventricle, and not just a single cross-section. These new and accurate imaging methodologies should enable the increasingly accurate evaluation of new therapeutic strategies to ameliorate infarct expansion, and greatly increase the sensitivity and accuracy of the identification and quantification of ventricular remodeling in patients.

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# Patency of the Infarct-Related Coronary Artery and Ventricular Geometry

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**The pathogenesis of acute myocardial infarction (AMI) involves a sudden thrombotic occlusion of a coronary artery. Spontaneous or pharmacologic thrombolysis may lead to myocardial salvage if patency is achieved within a narrow time window. However, patients in whom thrombolysis occurs late seem to demonstrate improved left ventricular (LV) function and prognosis, which may be independent of myocardial salvage. Preservation of normal LV geometry by reducing expansion of the infarcted segment is a likely mechanism for this benefit. Infarct expansion is most pronounced in patients with anterior wall AMI who have a persistently occluded infarct-related vessel. This process of expansion leads to early increases in LV volume and distortions of LV contour (abnormal LV geometry). Patients whose infarct segment is largest, patients who have manifested infarct expansion, and patients with a persistently occluded infarct-related artery are at highest risk for progressive LV dilation. Experimental data support the concept that reperfusion of occluded vessels that occurs too late for myocardial salvage will preserve LV geometry by limiting infarct expansion. Prospective clinical trials should address whether there is a late, "second time window" during which infarct expansion and distortions of LV geometry may be reduced by (1) therapy with thrombolytic agents applied late after infarction, (2) late mechanical reperfusion with percutaneous transluminal coronary angioplasty (PTCA) or related methods, and (3) load-reducing agents to decrease remodeling, such as angiotensin-converting enzyme inhibitors or nitroglycerin.**

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The last 15 years have brought a clearer understanding of the changes in the coronary arteries responsible for the development of acute myocardial infarction (AMI). In the vast majority of Q-wave AMIs, the initiation of the acute event is brought about by coronary thrombosis occurring on a fissured or ruptured atherosclerotic plaque, leading to total coronary occlusion and subsequent myocardial necrosis.[1-3] The appreciation of this sequence of events has brought with it an effort to limit infarct size by reestablishing coronary blood flow soon after the onset of chest pain to prevent the full extent of myocardial necrosis and preserve left ventricular (LV) function. Although mechanical reperfusion, with and without intracoronary thrombolysis, has been attempted with some notable successes,[4] the mainstay of coronary reperfusion remains intravenous thrombolytic therapy.[5,6] Experimental evidence, however, has shown that after coronary occlusion there is a rapidly moving wavefront of myocardial necrosis that proceeds from endocardium to epicardium, leading to completion of the infarction within 3 to 6 hours after occlusion.[7-10] Thus, the efforts to apply thrombolytic therapy to all otherwise eligible patients with infarction have been limited by the perception that for full benefit to occur, there is a only a narrow time window for treatment after the onset of chest pain.[11] The purpose of this review is to discuss the real possibility that this time interval may be extended to patients with longer periods of ongoing coronary occlusion.[12]

## THROMBOLYSIS AND LEFT VENTRICULAR FUNCTION

When thrombolytic therapy is used very early postinfarction, there is generally a demonstrable benefit in preservation of global LV function. Sheehan et al[13] reported that the ejection fraction measured by LV angiography showed a mild increase after thrombolysis (from 45.4% at baseline to 47.4% predischarge) only if reperfusion was attained prior to 4 hours after the onset of symp-

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toms. The increases in ejection fraction were due to improvement of wall motion in the infarcted area of the early-reperfusion group. Mathey et al[14] catheterized 69 patients who had been admitted less than 3 hours after the onset of transmural AMI and who had received thrombolytic therapy. Patients were recatheterized 2–3 weeks later, prior to hospital discharge. If thrombolytic therapy was initiated within 2 hours of the onset of symptoms, normal regional wall motion was found in 82% of patients. If treatment was delayed up to 5 hours, the probability of improved wall motion was reduced to 4[illegible]%. Serruys and associates[15] likewise found that when thrombolytic therapy was administered within 3 hours of AMI, regional function at the site of the infarct, as measured by contrast ventriculography 2–8 weeks after AMI, exhibited a significantly greater improvement than it did in patients receiving delayed therapy.

As expected, and presumably due to an improvement in overall LV function, a clear survival advantage has emerged for thrombolysis-treated patients in large trials.[16–19] However, since the beginning of the thrombolytic era, there have been inconsistent but intriguing reports that suggest that the benefits of successful reperfusion of the infarct-related vessel are not restricted to treatment during a fixed and narrow time window[20] and are not limited to patients who exhibit a measurable improvement in ejection fraction with a proportionate decline in mortality. Indeed, the modest improvements in ejection fraction associated with thrombolytic therapy would appear to be too small to account for large improvements in survival[21] (Table I). Examples of this phenomenon include the Tissue Plasminogen Activator: Toronto trial,[22] which compared tissue plasminogen activator (tPA) and placebo. Placebo group ejection fraction measured by radionuclide ventriculography 9 days after AMI was 48%, whereas the tPA group ejection fraction was 54%. It is difficult to attribute the reduction in mortality from 12.5% to 5.1% to this 6 point difference in ejection fraction within the low-normal range. White et al[23] compared treatment with streptokinase and placebo. The ejection fraction, measured by cardiac catheterization at 3 weeks was 53% for the placebo group and 58% for the streptokinase group. However, 30-day mortality was 12.5% in the placebo group and 3.7% in the treated group. An improvement in ejection fraction of 5% within the low-normal range again would not appear sufficient to account for such a striking improvement in survival.

**TABLE I** Angiographically Controlled Studies Showing Mortality Reduction but Small Magnitude Differences in Left Ventricular Ejection Fraction

| Study | Total No. Patients | Agent | No. Patients | LVEF | Early Mortality |
|---|---|---|---|---|---|
| TPAT[22] | 115 | Placebo | 56 | 48 | 12.5 |
| | | rt-PA | 59 | 54 | 5.1 |
| Interuniversity Study Group[5] | 533 | Placebo | 264 | 44 ± 15 | 10.0 |
| | | Streptokinase | 269 | 48 ± 15 | 5.0 |
| National Heart Study of Australia[76] | 144 | Placebo | 71 | 51 ± 15 | 10.0 |
| | | rt-PA | 73 | 53 ± 15 | 4.0 |
| White et al[23] | 219 | Placebo | 112 | 53 ± 13 | 12.5 |
| | | Streptokinase | 107 | 59 ± 10 | 3.7 |

Adapted from *Am J Med.*[21]
LVEF = left ventricular ejection fraction; rt-PA = recombinant tissue plasminogen activator; TPAT = Tissue Plasminogen Activator: Toronto.

## LATE SPONTANEOUS OR THROMBOLYTIC REPERFUSION

Spontaneous reperfusion of the infarct-related vessel, due to endogenous lytic mechanisms, occurs in a time-dependent fashion after AMI. This phenomenon is thought generally to occur too late for myocardial salvage. DeWood and associates[1] found that an occluded coronary could be demonstrated in 87% of patients with Q-wave AMI within 0–4 hours of the beginning of infarction. The incidence of complete occlusion decreased to 65% in patients studied 12–24 hours after infarction. This time-dependent decrease in the incidence of occluded infarct-related vessels is presumably due to spontaneous clot lysis. Indeed, the 13% of infarct-related arteries patent in the earliest phase of the infarction might represent vessels that had been totally occluded earlier and had opened spontaneously by the time the angiograms were performed. Similar data on spontaneous thrombolysis have been obtained in the placebo arms of thrombolytic therapy trials. Coronary angiography of placebo-treated patients (carried out 2–8 weeks following AMI) revealed a patency rate of 52% for the infarct-related vessel in the study reported by Serruys et al.[15] White et al[23] reported a similar (54%) placebo group coronary patency rate 3 weeks after infarction. Thus, although spontaneous reperfusion of the infarct-related vessel occurs in about one half of patients with AMI, such reperfusion might be expected to occur too late for myocardial salvage, and, therefore, clinical benefits from such late reperfusion might not be expected. However, retrospective analyses of clinical data suggest the reverse to be true.

Cigarroa et al[24] reported on 179 patients after AMI who had single-vessel coronary artery disease. Patients were divided into those with partial or complete antegrade flow (36%) and those with no or minimal antegrade flow (64%). This classification was based on catheterization data obtained an average of 27 days after AMI. Baseline data, including LV volumes and ejection fraction, were nearly identical in both groups. The duration of follow-up ranged from 10 to 124 months. A multivariate analysis demonstrated that the independent predictors of mortality were: status of antegrade flow in the infarct-related vessel, LV end-systolic volume, and the left anterior descending coronary as the infarct-related vessel (Figure 1).

Similar results have been reported by Schroder and coworkers[25] on 368 patients from the Intravenous Streptokinase and Myocardial Infarction (ISAM) study. An analysis was reported of patients who had no evidence for early reperfusion as manifested by a late peaking serum creatine kinase MB time–activity curve. Contrast angiography was obtained 1 month after AMI and the infarct-related artery was found patent in 58% of patients. A patent infarct-related artery was associated with better LV function at the catheterization 1 month after AMI (ejection fraction in the group with a patent vessel was 56%; in the group with an occluded vessel, 50%). In patients with anterior infarctions, mortality at an average follow-up of 31 months was 28% for patients with an occluded left anterior descending coronary artery, versus 8% for patients with a patent vessel. The difference in ejection fraction between these groups (patent artery, 53% ejection fraction; occluded artery, 44% ejection fraction) was not of sufficient magnitude to account for this marked difference in mortality.

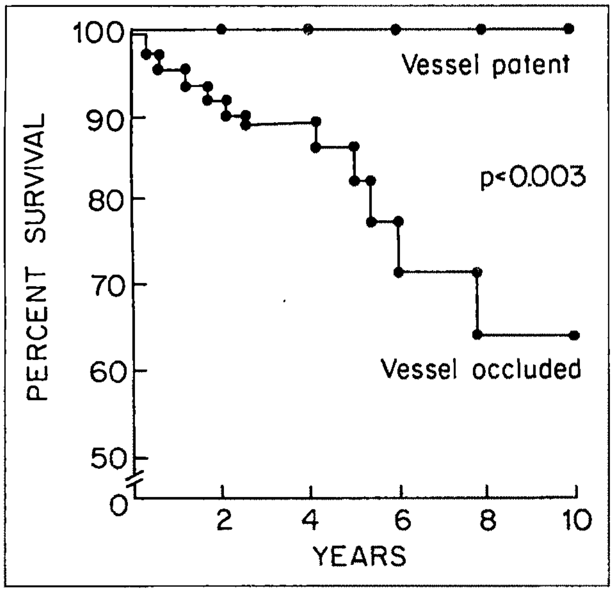

**FIGURE 1. Survival analysis of patients with patent and occluded infarct-related arteries. (Reprinted from *Am J Cardiol.*[24])**

## LATE THROMBOLYSIS AND SURVIVAL

Observations from thrombolytic trials in which therapy was administered beyond the critical time for myocardial salvage supports the importance of patency of the infarct-related vessel. The apparent benefits of late reperfusion may translate to a survival benefit for patients receiving thrombolytic therapy after the traditional 4-hour time window has elapsed. Subgroup analyses of several prospective studies have reported favorable results for comparatively late thrombolysis. The Western Washington Randomized Trial[26] of intracoronary streptokinase reported a 68% coronary reperfusion rate an average of 5 hours after the onset of the AMI without demonstrating an improved ejection fraction. Nevertheless, 30-day and 6-month mortality were significantly lower in the streptokinase group than in the placebo group. The Thrombolysis in Myocardial Infarction (TIMI) I trial initiated thrombolytic therapy an average of 4.5 hours after the onset of symptoms.[27–29] Thrombolytic reperfusion occurred > 4 hours after the onset of symptoms in 64% of patients. Patients with a patent infarct-related vessel demonstrated a trend toward a lower 6-month mortality (vessels patent, 5.6%; vessels occluded, 12.5%) and 12-month mortality (vessels patent, 8.1%; vessels occluded, 14.8%; $p = 0.07$).[29]

The Second International Study of Infarct Survival (ISIS-2) evaluated thrombolysis with streptokinase and aspirin up to 24 hours after infarction in 17,187 patients.[18] Among patients enrolled 0–4, 5–12, and 13–24 hours after the onset of symptoms, the streptokinase-associated reductions in the odds of vascular death 5 weeks after AMI were 35%, 16%, and 21%, respectively. However, benefits of late thrombolysis have not been consistent across different studies. The Gruppo per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) study[16] reported no survival benefit for patients receiving thrombolysis 6–12 hours after the onset of infarction. However, the number of patients treated in this time interval may have been too small to test this question adequately. Grines and DeMaria[5] reviewed published data on late thrombolysis and found that a summation of published data strongly suggests a survival benefit for patients receiving late thrombolysis (Table II). These intriguing findings have led investigators to postulate mechanisms whereby attaining a patent infarct-

**TABLE II** Mortality of Patients Receiving Thrombolysis 12 to 24 Hours Post-myocardial Infarction Onset

| | No. Deaths (%) | | |
|---|---|---|---|
| Study | Thrombolysis | Control | p Value |
| Yusuf et al[20] | 44/354 (12.4) | 84/383 (21.9) | 0.0007 |
| ISIS-II[18] | 106/1,224 (8.7) | 132/1,227 (10.8) | 0.08 |
| Pooled | 150/1,578 (9.5) | 216/1,610 (13.4) | 0.002 |

Adapted from *J Am Coll Cardiol.*[5]
ISIS-II = Second International Study of Infarct Survival.

related artery too late for myocardial salvage might still lead to improved survival.[6,12,30,31] The most likely potential mechanism is prevention of LV distortion early after AMI with resulting attenuation of late LV dilation. Another important possible mechanism includes promotion of electrical stability in the reperfused infarct.

**Experimental evidence favoring late reperfusion:** Hochman and Choo[32] induced AMIs in rats by ligating the anterior descending coronary artery. Some animals had a permanent coronary ligation, whereas others had either early (30 minutes) or late (2 hours) coronary reperfusion. The animals were studied 6 weeks later, after the infarct had healed completely. As anticipated, infarcts were smaller in the animals with early reperfusion. The infarct size and extent of infarct transmurality of animals with late reperfusion or permanent occlusion were not different. However, the late (2-hour) reperfusion group demonstrated an extent of infarct expansion that was comparable to that of the early reperfusion group and much less than that of the permanent occlusion group (Figure 2). Hale and Kloner[33] noted, also in the rat, that late reperfusion resulted in a thicker scar and less infarct expansion than did a permanent coronary occlusion (Figure 3). Althaus et al[34] reported that in pigs, reperfusion after 1 hour led to the same infarct size as did permanent coronary occlusion. However, the reperfused group had less aneurysmal LV dilation detected at 1 week. This benefit on LV geometry was ascribed by the investigators to more effective healing of the infarct in the reperfused group, suggesting greater strength of the reperfused myocardial scar.

Reperfused infarcts may demonstrate subendocardial hemorrhage, and a reduction in infiltration with polymorphonuclear leukocytes, but generally a similar hydroxyproline content when compared with nonreperfused infarcts.[35] The effect of late reperfusion on the tensile strength of the myocardial scar was studied by Connelly et al.[36] In contrast to the study by Althaus et al,[34] these investigators found that late reperfused scars in the infarcted rabbit were similar to nonreperfused scars with respect to hydroxyproline content and fibrous tissue composition. Further, at physiologic stress levels, there were no differences in strain, stiffness, creep, and stress relaxation among groups of reperfused or nonreperfused infarcts. Thus, the beneficial effects of late reperfusion may occur during a time window prior to the beginning of scar formation, while the infarct is still "soft."

Force and coworkers[37] created experimental AMIs in dogs by ligation of the circumflex coronary

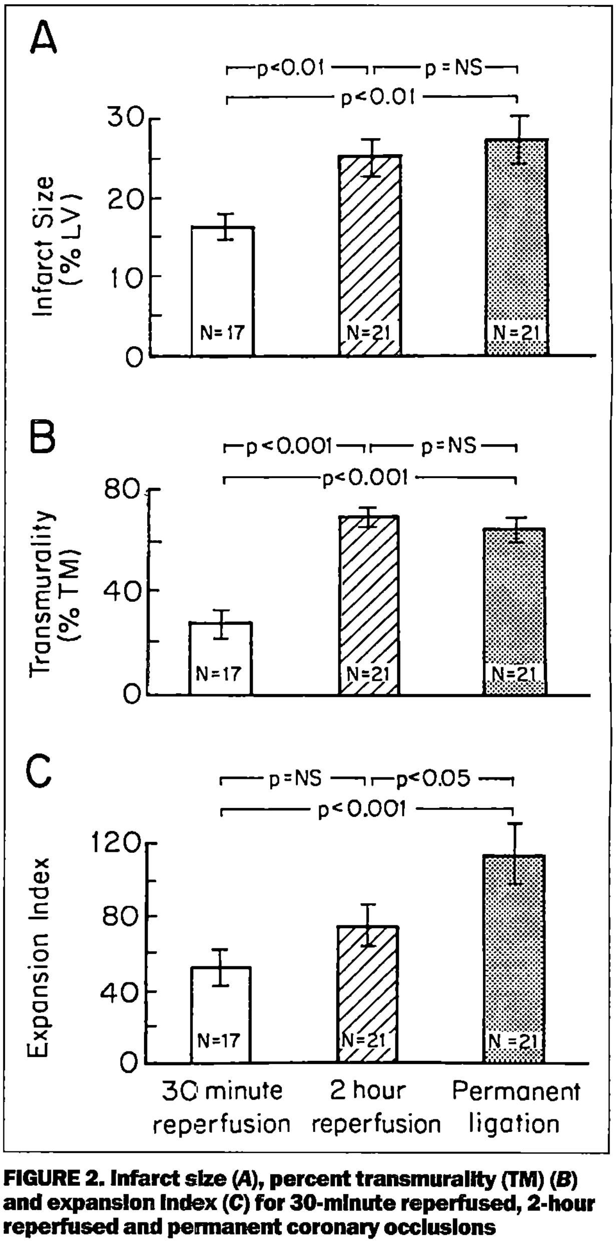

**FIGURE 2. Infarct size (*A*), percent transmurality (TM) (*B*) and expansion index (C) for 30-minute reperfused, 2-hour reperfused and permanent coronary occlusions (mean ± standard error of the mean) in the rat. Expansion index is defined as: (left ventricular [LV] cavity area/total heart area) × (uninfarcted wall thickness/infarcted wall thickness). NS = not significant. (Reprinted with permission from *Circulation.*[32])**

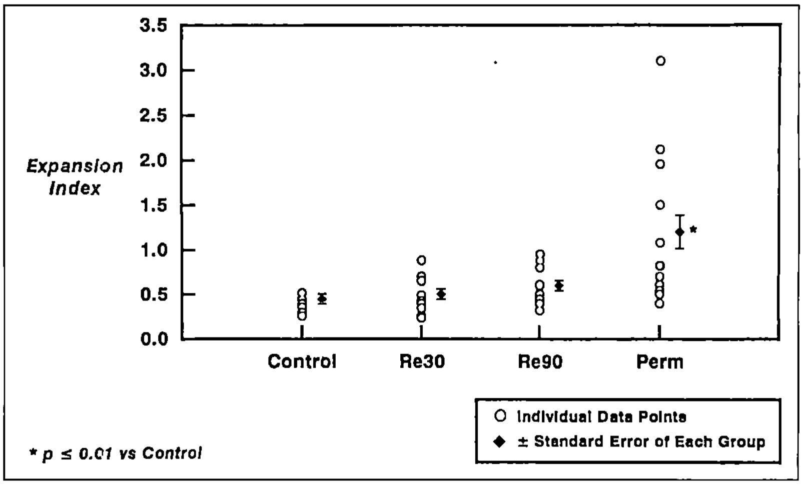

**FIGURE 3. Left ventricular changes with reperfusion after acute myocardial infarction. Data are represented as individual points (open circles) and means ± standard error of the mean (dark diamonds) and demonstrate expansion index in rats without coronary occlusion (control); reperfusion after 30 minutes and 90 minutes of occlusion (Re30 and Re90, respectively); and permanent occlusion (Perm). Even though reperfusion at 90 minutes does not salvage myocardium, there is less infarct expansion than with a permanent occlusion. (Reprinted with permission from *Am Heart J*.[33])**

artery and studied the early, reversible phase of infarct expansion. In their preparation, reperfusion took place 3, 4, 6, or 8 hours later. Infarct size and transmurality were similar among all 4 groups studied. Delayed reperfusion produced an immediate decrease in infarct expansion, measured as a return toward normal of the geometry of the infarcted segment. Late reperfusion was also associated with a reduction in end-diastolic cavity area (which correlates closely with LV volume) (Figure 4). Brown et al[38] reported an improvement in LV geometry with reperfusion that was independent of myocardial salvage in a dog model. Immediately after delayed reperfusion, early infarct dilation was reversed. This was followed by increasing stiffness of the infarct segment and a partial normalization of LV volume. These investigators concluded that the infarct thins and dilates maximally immediately after occlusion, and that delayed reperfusion reverses these immediate changes without the need for myocardial salvage.

Since, as noted before, the fibrous tissue composition, hydroxyproline content and tensile strength of the postinfarction scar tissue is similar in the reperfused and nonreperfused infarcts, Pirzada et al[39] and Brown et al[38] have speculated that the immediate reversal of infarction-induced dilation by reperfusion is due to calcium activation of the actomyosin complex, leading to contracture and contraction band necrosis and, therefore, less infarct expansion. This hypothesis rejects the concept that delayed reperfusion may be beneficial by preventing late, progressive infarct expansion due to creep of the necrotic segment or scar and suggests a second time window measured in hours beyond which even delayed reperfusion may not be beneficial. In addition, these experimental studies suggest that the proposed improvements in LV geometry of late reperfusion could be tested in the clinical setting.

Finally, there is experimental evidence showing that early infarct expansion in the dog is dependent not only on the extent of myocardial necrosis, but also on the site of infarction. Picard and coworkers[40] have analyzed the extent of early infarct expansion measured 10 minutes following occlusion of the left anterior descending or the left circumflex coronary arteries. These investigators found that despite a similar extent of wall motion abnormality, the left anterior descending occlusion group had a greater increase in echocardiographically derived endocardial surface area (28.4 ± 13.6 $cm^2$) than did the circumflex occlusion group (5.2 ± 2.5 $cm^2$). This interesting observation of the differential effects of infarct location on LV shape, as mediated by infarct expansion, may partially

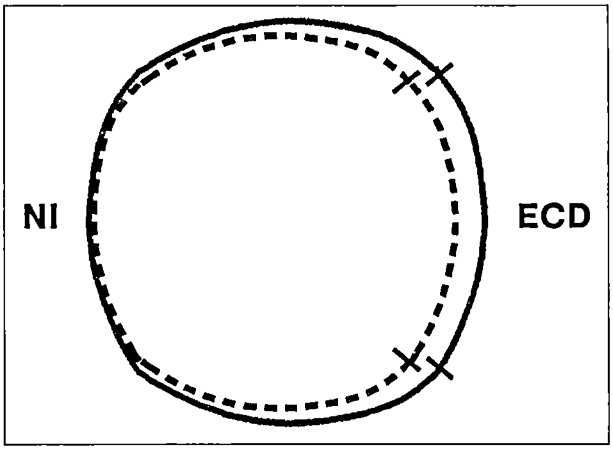

**FIGURE 4. Schematic drawing of end-diastolic endocardial outline before reperfusion (solid outline) and after late reperfusion (dotted line) constructed from the mean values for 17 study dogs undergoing circumflex coronary artery occlusion. NI = normal region; ECD = echocardiographic contrast defect (infarcted region). (Reprinted with permission from *J Am Coll Cardiol*.[37])**

**TABLE III** Analysis of 64 Patients Without Thrombolysis

| | Patent LAD (n = 25) | Occluded LAD (n = 39) | p |
|---|---|---|---|
| Age (yrs) | 54 ± 12 | 55 ± 10 | NS |
| Days | 18 ± 6 | 18 ± 5 | NS |
| CK peak (IU) | 2296 ± 2340 | 2917 ± 1267 | NS |
| RVG-EF (%) | 35 ± 11 | 31 ± 9 | NS |
| Q-wave sum | 4 ± 1 | 5 ± 2 | NS |
| LV EDP (mm Hg) | 19 ± 7 | 21 ± 7 | NS |
| EDV (ml) | 218 ± 54 | 249 ± 49 | <0.02 |
| ESV (ml) | 123 ± 49 | 152 ± 47 | <0.02 |
| DSI (%)* | 34 ± 6 | 40 ± 6 | <0.002 |
| SSI (%)* | 25 ± 7 | 29 ± 6 | <0.05 |
| Akinesis (%)† | 13 ± 11 | 13 ± 8 | NS |
| Dyskinesis (%)† | 10 ± 9 | 17 ± 8 | <0.002 |

*Sphericity index[61] is a measure of how spherical a ventricle is. It is calculated by dividing the true LV volume by the volume of an imaginary sphere that was constructed using the longest axis of the LV as its diameter.

†Wall motion abnormality is calculated as the percentage of the overall LV diastolic perimeter that is akinetic or dyskinetic during systole.

CK = creatine kinase; DSI = diastolic sphericity index; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; RVG = radionuclide ventriculogram; SSI = systolic sphericity index.

explain the disproportionately adverse prognosis of anterior infarctions.[41] Ultimately, clinical interventions with late reperfusion therapy may need to be tailored to those groups most likely to sustain early and late LV shape changes.

## LEFT VENTRICULAR GEOMETRY AND THE OCCLUDED INFARCT-RELATED VESSEL

Animal experiments[42–44] as well as clinical observations have established that the LV may dilate after AMI, a process often termed "LV remodeling." This process begins in the acute period as infarct expansion, or thinning and lengthening of the infarct segment, and continues in the late convalescent period with lengthening of the noninfarcted segment.[45–50] These changes in the lengths of the specific components of the infarcted ventricle are associated with changes in the shape of the LV cavity.[51] Indeed, both Pirolo et al[52] and Jugdutt and Michorowski[53] have defined infarct expansion by its alteration of regional LV shape. Characteristics of the infarct-related vessel are important in determining the extent of abnormality of LV shape. Approximately 80% of patients with the most severe LV shape distortion had a totally occluded infarct related vessel at catheterization approximately 2 weeks after AMI.[54]

We performed a reanalysis of 64 patients who had sustained a Q-wave anterior wall AMI, and who had received neither mechanical nor thrombolytic reperfusion. Patients were catheterized an average of 17 days after AMI (Table III) and divided on the basis of present or absent infarct-related vessel flow. An occluded left anterior descending coronary artery was present in 39 of 64 (61%) patients. Patients with occluded and patent infarct-related vessels had similar peak creatine kinase, total number of Q-waves developed, and radionuclide ejection fraction. However, quantitative ventriculography revealed that patients with an occluded infarct-related vessel showed marked abnormalities of LV size, function, and shape[54] when compared with those with a patent vessel.

Other retrospective clinical data also suggest that the occluded infarct-related vessel is associated with infarct expansion and with the resulting chronic abnormalities of LV shape. Hirai et al[55] found that 7 of 12 patients who had a persistently occluded infarct-related artery without collateral filling despite intracoronary thrombolytic therapy developed LV aneurysms. In contrast, only 1 of 25 patients with successful reperfusion developed an LV aneurysm as defined on repeat catheterization an average of 35 days after the acute study. Patients with occluded vessels at baseline who did not develop LV aneurysms were noted on a late catheterization to have developed either spontaneous reperfusion or collateral filling of the infarct-related vessel. Forman et al[56] studied 79 patients after anterior wall AMI and noted that in the 52 patients with a persistently occluded left anterior descending coronary artery, 25 (48%) had developed LV aneurysms. In contrast, only 4 of 27 patients (15%) with a patent left anterior descending coronary artery developed an LV aneurysm. Touchstone et al[57] reported a small series of patients who received streptokinase <4 hours after infarction. There were 15 patients whose regional LV function did not improve on postinfarct echocardiograms, and, of these, 27% developed infarct expansion. An occluded infarct-related vessel was present in all 4 patients who developed expansion and in only 1 of 11 (9%) patients who did not develop expansion. The investigators concluded that when infarct expansion occurred after thrombolytic therapy, it was likely that an occluded infarct-related artery was present.

LV shape abnormalities after infarction may independently portend a poor prognosis. Distortion of the normal ellipsoidal LV shape by infarct expansion is associated with LV aneurysm formation,[58] cardiac rupture[59] and is a mechanism for early LV enlargement. An apical–anterior LV shape deformity occurring early, prior to fibrosis and formation of a classic LV aneurysm, has been termed an "expaneurysm."[58] Meizlish and coworkers[58] showed this early shape deformity, detected by radionuclide ventriculography, to be an extremely important predictor of early mortality following anterior AMI. Patients who developed severe LV shape abnormalities prior to hospital discharge had a 61% 1-year mortality, whereas patients without severe LV shape distortion manifested only a 9% mortality. These investigators postulated that the abnormalities in LV contour observed were due primarily to infarct expansion.

Physiologic considerations[60] and clinical studies[58,61] suggest that LV shape is an important descriptor of LV structure and function and of clinical outcome. An analysis of left ventriculograms in patients with anterior infarctions[54] demonstrated that LV shape, as defined by the pattern recognition method described by Meizlish et al,[58] was an important correlate of LV volumes, ejection fraction, and filling pressures and was an independent predictor of the formation of LV mural thrombi. Patients with the most spherical left ventricles after anterior wall AMI demonstrated the poorest exercise capacity and functional class and were most likely to develop congestive heart failure.[61] Thus, LV shape distortion is clinically undesirable and constitutes an additional consequence of infarct expansion. These unfavorable effects may be due to increases in regional wall stress from altered endocardial curvature and/or to alterations in fiber orientation, leading to disruption of the normal contractile pattern[62] and contractile dysfunction greater than expected from the extent of infarction alone.

The association of infarct expansion and LV geometric distortion with the persistently occluded infarct-related vessel may have long-term sequelae as well. Erlebacher et al[63] followed patients sequentially with echocardiography after AMI and, as expected, found that some patients developed infarct expansion. Those patients with infarct expansion were found to be at highest risk for late LV enlargement. Lamas and Pfeffer[48] studied 55 patients an average of 21 months following a first and only anterior AMI. Patients' diastolic and systolic LV volumes were closely related to the extent of wall motion abnormality. For example, for patients with a mild, moderate, or severe extent of wall motion abnormality, LV end-diastolic volume increased 17%, 61%, and 151% above that of patients with no wall motion abnormality. The extent of wall motion abnormality, expressed as the percentage of the diastolic perimeter that is akinetic or dyskinetic, correlates with the extent of LV dilation. Thus, the occluded infarct-related vessel may indirectly lead to chronic LV dilation because expansion of an infarcted segment may lead to a functionally greater degree of wall motion abnormality for a given infarct size. The patients in whom the unfavorable wall stress and loading conditions are most severe are those who enter the vicious cycle of progressive LV enlargement.

A direct link between the occluded infarct-related vessel and LV dilation has been described by Jeremy and coworkers[64] (Figure 5). These investigators studied patients following AMI by means of radionuclide techniques within 48 hours of AMI and again at 1 month and related the presence or absence of progressive LV enlargement to the status of the infarct-related vessel as determined by cardiac catheterization prior to hospital discharge. The sole coronary anatomic predictor of progressive LV dilation was an occluded infarct-related vessel without collateral filling at the time of predischarge catheterization.

Lavie et al[65] noted that progressive LV dilation could be prevented by successful thrombolysis. Pfeffer and coworkers[66] noted that a persistently occluded infarct-related vessel approximately 3 weeks after an anterior wall AMI was a major risk factor for future, late, LV dilation. Mitchell et al[50] reported that late dilation is not due to additional expansion of the akinetic or dyskinetic segment, but to lengthening of the contractile segment, presumably due to volume overload hypertrophy of the noninfarcted segment. Thus, the persistently occluded infarct-related vessel, through its association with infarct expansion, leads to unfavorable local and global LV geometry. These early shape and volume abnormalities appear to cause the abnormal increases in internal loading conditions that lead to volume overload hypertrophy of the contractile segment and to late increases in LV volume.

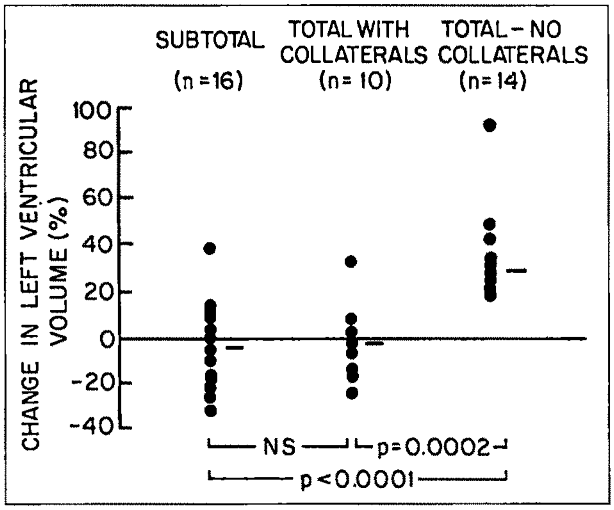

**FIGURE 5. Relation of infarct-artery perfusion and left ventricular volume change in the month after myocardial infarction. NS = not significant. (Reprinted with permission from *J Am Coll Cardiol*.[64])**

## ELECTROPHYSIOLOGIC EFFECTS OF CORONARY PATENCY

The improvement in survival suggested for late thrombolysis may be related to beneficial electrophysiologic effects in the patient after AMI. Reperfusion using streptokinase has been associated with a diminution of arrhythmias induced by programmed stimulation.[67] However, this association was confounded by a superior ejection fraction in patients treated with thrombolysis. Sager et al[68] evaluated a small number of patients with a recent transmural anterior wall AMI and LV contour deformities consistent with LV aneurysm formation. The infarct-related vessel was patent in 75% of the thrombolysis-treated patients. Sustained monomorphic ventricular tachycardia could be induced in 12% of the thrombolysis-treated patients and in 88% of the nonthrombolysis-treated patients.

The presence of late potentials on the signal-averaged electrocardiogram of the patient after AMI is considered a risk factor for significant cardiac arrhythmia. Patients with an occluded infarct-related vessel are likely to demonstrate late potentials. McClements and colleagues[69] reported on 123 patients with AMI, of whom 95 (77%) had received thrombolytic therapy. The specificity of late potentials recorded within 48 hours or on day 6 for an occluded infarct-related artery was 76% and the sensitivity was 66%. If a patient was free of late potentials 6 days after AMI, there was an 84% chance that the patient had a patent infarct-related vessel. Gang and coworkers[70] studied 106 patients admitted with a first AMI. Thrombolysis with tPA was administered within 4 hours in 44 patients. The remaining 62 patients did not receive thrombolytic therapy. In the thrombolysis-treated group, late potentials, recorded within 48 hours of admission, were present in only 5% of patients. However, 23% of patients in the nonthrombolysis group demonstrated late potentials. The apparent reduction in the incidence of late potentials by thrombolytic therapy was closely related to the patency of the infarct-related vessel. Only 6% of patients with a patent infarct-related vessel had late potentials, whereas 32% of those with an occluded vessel had late potentials recorded. Thus, the patient with a completed infarct and a patent infarct-related vessel appears to demonstrate a reduction in arrhythmia potential.

## PROSPECTIVE TRIALS

Preliminary results of prospective clinical trials have not yet led to definitive recommendations regarding late thrombolytic or mechanical reperfusion. The sixth Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI)-6[71] trial randomized 197 patients to therapy with tPA or placebo beginning 6–24 hours after symptom onset. Baseline catheterization was performed an average of 36 hours after infarction, and patients with a persistently occluded infarct-related vessel were re-randomized to receive angioplasty or no angioplasty. At baseline catheterization, infarct-vessel patency for tPA-treated patients was 64% and 28% for the placebo-treated group. However, ejection fraction was similar (tPA group, 47.5%; placebo group, 48.5%), and inhospital mortality was also similar (9.6% vs 9.0%). At follow-up catheterization 6 months after admission, neither ejection fraction (52.5% vs 51.6%) nor infarct-vessel patency status (54% vs 51%) were different between

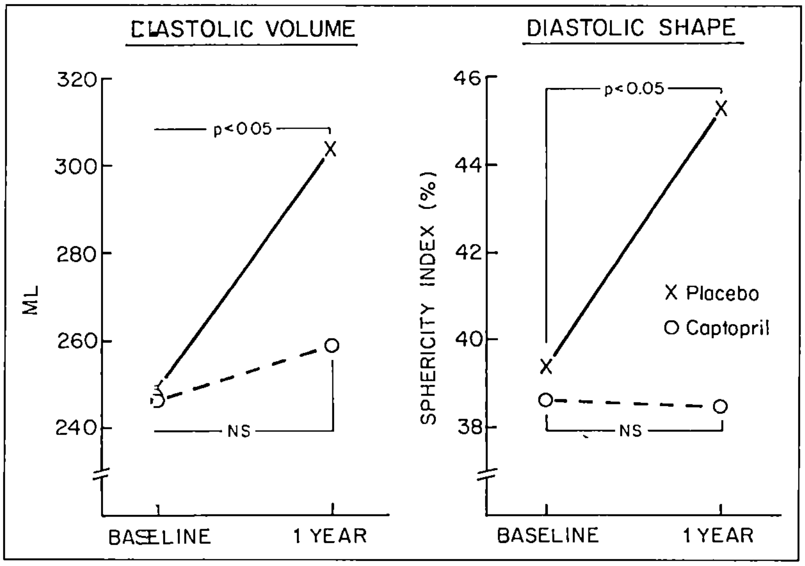

**FIGURE 6. The effect of load-reducing therapy with captopril on the left ventricular diastolic volume and shape of patients with a large infarct and an occluded infarct-related artery. NS = not significant. (Reprinted with permission from *Am Heart J.*[51])**

those groups. However, placebo-treated patients demonstrated a 25% increase in LV volumes, whereas treated patients demonstrated stable LV volumes.[72] Final reports of TAMI-6 should provide information on more sophisticated measures of ventricular size and shape.

The Estudio Multicentrico Estreptoquinasa Republica Argentina trial randomized 3,600 patients 7–24 hours postinfarction to receive placebo or streptokinase therapy.[73] Preliminary reports suggested a small survival benefit only in the patients receiving streptokinase between 7 and 12 hours after MI.[73] Finally, preliminary results from a small Japanese trial[74] reported that late reperfusion (> 6 hours after AMI onset) was associated with end-diastolic volumes that were 29% smaller than those of the nonreperfused group.

## POTENTIAL DIRECTIONS IN THERAPY

Currently available data suggest that coronary reperfusion beyond the classic time window of 6 hours may be desirable and lead to preservation of LV geometry with improved survival. However, this "open vessel hypothesis" requires critical prospective analysis. Definitive clinical trials still need to address the comparative benefits on infarct expansion and LV geometry of therapy with thrombolytic agents applied late after infarction, late mechanical reperfusion with percutaneous transluminal coronary angioplasty, coronary artery bypass graft or other methods, load-reducing agents to decrease remodeling,[66,75] such as angiotensin-converting enzyme inhibitors (Figure 6) or nitroglycerin, and therapies combining late reperfusion and load reducing therapy. In addition, the concept of a "second time window" during which late reperfusion may be of benefit, as well as the specific patient population to target with expanded indications for thrombolysis or angioplasty, will need future definition with randomized clinical trials.

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# Intravenous Nitroglycerin Unloading in Acute Myocardial Infarction

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**Low-dose intravenous nitroglycerin infusion can be safely administered during acute myocardial infarction to unload the left ventricle and salvage ischemic myocardium and left ventricular geometry and function. In an experimental conscious dog model, low-dose infusion titrated to decrease mean blood pressure by 10% over the first 6 hours after coronary artery ligation resulted in 51% decrease in infarct size, 54% decrease in preload, and more than 50% increase in collateral blood flow. The same benefits were seen when methoxamine was given to counteract that 10% decrease in blood pressure. Similar short-term nitroglycerin infusion also limited remodeling in the dog model. More important, no myocardial salvage was seen with excessive nitroglycerin-induced hypotension to levels <80 mm Hg. Clinically, prolonged low-dose nitroglycerin infusion was evaluated in a prospective, randomized, single-blinded, placebo-controlled study of 310 patients with acute infarction: 154 received nitroglycerin and 156 received placebo. Nitroglycerin was titrated to reduce mean blood pressure by 10% in normotensive patients and up to 30% in hypertensive (blood pressure >140/90 mm Hg) patients, but not to <80 mm Hg. Nitroglycerin produced several benefits compared with placebo: (1) smaller creatine kinase infarct size; (2) less regional left ventricular dysfunction, better global ejection fraction, and less infarct expansion and thinning; (3) better clinical functional status and hemodynamics; (4) fewer inhospital complications such as acute left ventricular failure and dilation due to marked infarct expansion, left ventricular thrombus, cardiogenic shock, and infarct extension; and (5) fewer deaths up to 1 year in patients with anterior Q-wave infarction.**

**(Am J Cardiol 1991;68:52D–63D)**

Intravenous nitroglycerin unloading in acute myocardial infarction (AMI) was considered dangerous until the late 1970s because of the risk of severe hypotension and reflex tachycardia.[1,2] When nitrates were proposed for therapy in congestive heart failure, the focus was on chronic reduction of left ventricular impedance and afterload.[3–5] As a result, high doses and long-acting preparations were favored.[3–5] In contrast, the aim of nitrate unloading in AMI during the mid to late 1970s was mainly to reduce the elevated preload in patients with left ventricular failure or pulmonary edema without producing such marked reduction of afterload that might cause excessive hypotension and extension of ischemic injury.[6–10] Intravenous nitroglycerin infusion was preferred in most studies[6–10] because its rapid onset and offset of action permitted more cautious administration, with accurate dose titration and prompt withdrawal of pharmacologic effect in the event of undesirable side effects. This article reviews the evidence that unloading of the left ventricle with low-dose intravenous nitroglycerin infusion can be applied safely during AMI to salvage ischemic myocardium, left ventricular geometry and function,[11–14] and improve clinical outcome.[11–15]

## MECHANISMS

Nitrates act primarily by causing vasodilation (Figure 1). Dilation of venous and arterial vascular beds results in left ventricular unloading via a decrease in preload and afterload. Dilation of the coronary vascular bed is the primary cause of increased coronary blood flow. However, coronary flow and the myocardial distribution of flow are influenced by the decrease in preload and afterload.

The underlying mechanism at the cellular and molecular level is direct relaxation of vascular smooth muscle. Needleman and Johnson[16] pro-

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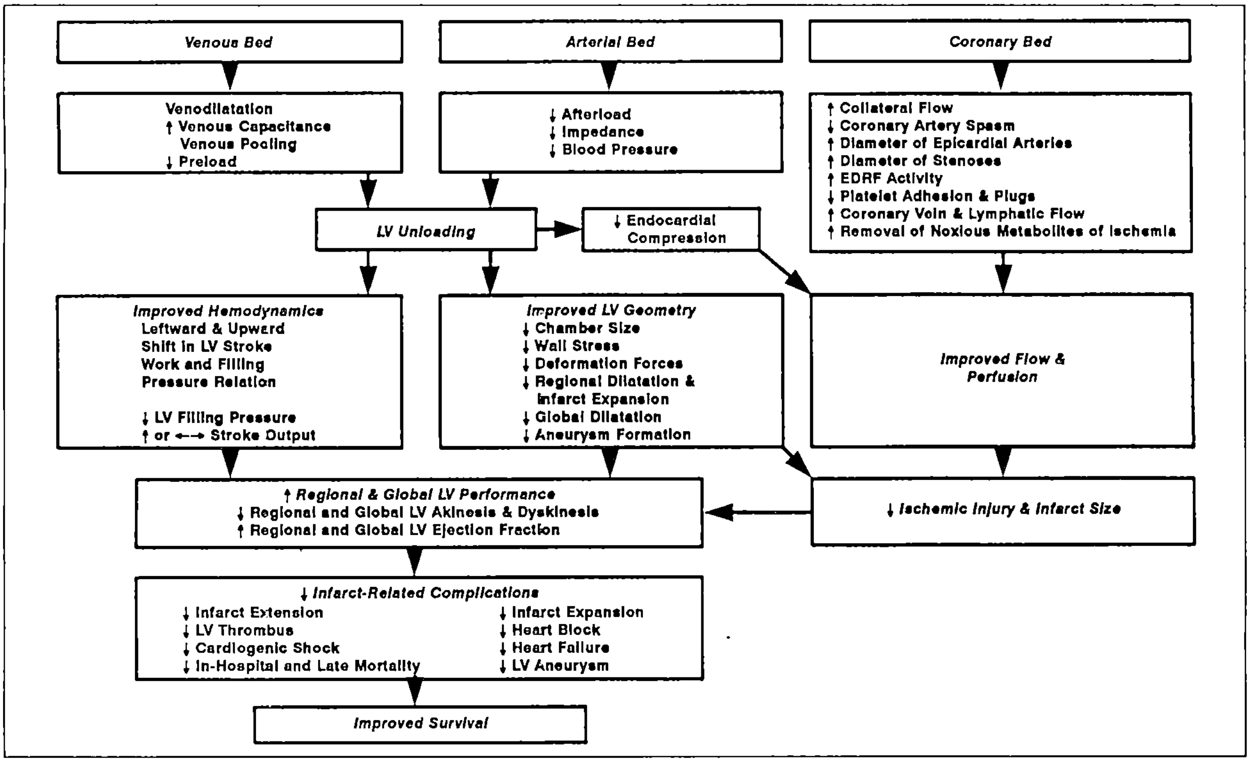
posed that exogenous nitrates interact with key sulfhydryl groups in specific nitrate receptors, thereby triggering denitration, oxidation of the sulfhydryl group, and relaxation. These authors also equated oxidation of the sulfhydryl group in the nitrate receptor with reduced affinity or tolerance.[16] Later, Ignarro et al[17] proposed a cascade involving intracellular biotransformation, metabolic activation to nitric oxide, S-nitrosothiol formation, activation of guanylate cyclase, increase in cyclic guanosine monophosphate formation, modified calcium ion traffic, and relaxation. Recently, Palmer et al[18] proposed that endothelium-derived relaxation factor (EDRF), which mediates the action of nitro vasodilators, might be nitric oxide and represent an "endogenous nitrate." A secondary mechanism for nitrate-induced relaxation is via prostacyclin ($PGI_2$) release by the endothelium.[19]

**Vasodilation and dose:** The pharmacologic fact that the effect of nitrates on different vascular beds is nonuniform and dose-related[20–22] has important pathophysiologic and therapeutic implications in AMI.[11] First, the sensitivity of vascular smooth muscle is greater in venous than arterial beds, and maximal venodilation is achieved at very low doses with nitroglycerin concentrations $<0.2$ ng/ml.[20] Higher doses decrease afterload without further decreases in preload.[20] This implies that left ventricular preload might be maximally reduced very early during incremental dose titration, with little further decrease at higher doses.

Second, arterial conductance vessels dilate at low dose and arteries at high dose.[20–22] Increasingly higher doses, therefore, decrease left ventricular impedance and afterload, blood pressure, and systemic vascular resistance. Of practical importance is the recent demonstration that profound left ventricular unloading with decrease in left ventricular impedance and afterload is achieved in patients even before a detectable decrease in arm blood pressure can be measured by the standard sphygmomanometer.[23]

Third, dilation of native intramural coronary collateral vessels and increased collateral flow is seen with low doses of nitroglycerin.[24–26] The marked decrease in preload at low doses is associated with decreases in filling pressure, ventricular wall tension, and subendocardial compression, which also result in increased flow in intramural vessels and improved myocardial distribution of flow. Bassenge and Stewart[22] elegantly showed in the dog model that nitroglycerin dilates veins and coronary arteries at very low doses (0.5 μg/kg/min), peripheral arteries at 10-fold higher doses (5 μg/kg/min), and myocardial resistance vessels at 40-fold higher doses (20 μg/kg/min).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↓ Coronary Artery Spasm
↑ Diameter of Epicardial Arteries
↑ Diameter of Stenoses
↑ EDRF Activity
↓ Platelet Adhesion & Plugs
↑ Coronary Vein & Lymphatic Flow
↑ Removal of Noxious Metabolites of Ischemia
LV Unloading
↓ Endocardial Compression
Improved Hemodynamics
Leftward & Upward Shift in LV Stroke Work and Filling Pressure Relation
↓ LV Filling Pressure
↑ or ←→ Stroke Output
Improved LV Geometry
↓ Chamber Size
↓ Wall Stress
↓ Deformation Forces
↓ Regional Dilatation & Infarct Expansion
↓ Global Dilatation
↓ Aneurysm Formation
Improved Flow & Perfusion
↑ Regional & Global LV Performance
↓ Regional and Global LV Akinesis & Dyskinesis
↑ Regional and Global LV Ejection Fraction
↓ Ischemic Injury & Infarct Size
↓ Infarct-Related Complications
↓ Infarct Extension
↓ LV Thrombus
↓ Cardiogenic Shock
↓ In-Hospital and Late Mortality
↓ Infarct Expansion
↓ Heart Block
↓ Heart Failure
↓ LV Aneurysm
Improved Survival

**FIGURE 1. Mechanisms of action of nitroglycerin in acute myocardial infarction. EDRF = endothelium-derived relaxation factor; LV = left ventricular.**

Fourth, high doses of intravenous nitroglycerin required to decrease mean arterial pressure by >10% (range 17–45%) to levels below an average of 83 mm Hg (and down to 58 mm Hg) during AMI in the dog model decreased perfusion pressure and abolished beneficial effects on collateral blood flow and infarct size.[26] Such high doses produce excessive vasodilation and loss of ability for coronary autoregulation, so that myocardial perfusion becomes exquisitely dependent on driving perfusion pressure.[26]

Fifth, continuous exposure to high doses and concentrations of nitrates for several days consistently produce tolerance with attenuation of vasodilator effects and smooth muscle relaxation.[27–29] In contrast, tolerance with low dose intravenous nitroglycerin infusion for 48 hours in AMI is partial and infrequent, and does not abolish the beneficial effects.[30]

## SALVAGE OF MYOCARDIUM

A major potential benefit of controlled nitrate-induced vasodilation in AMI is myocardial salvage. Thus, it favorably modifies cellular energetics by decreasing myocardial oxygen demands and increasing supply, thereby decreasing ischemic injury and infarct size.[1,14,25] At low doses, nitroglycerin acts predominantly as a venous and coronary artery dilator. The decrease in myocardial oxygen demand is therefore mediated mainly via a sequence of venodilation, increased venous capacitance, reduced right ventricular size, reduced left ventricular preload, decreased left ventricular size, decreased wall tension, and decreased wall stress.[11,31] Although less marked at low dose, arterial dilation decreases left ventricular impedance and afterload, which also results in decreased left ventricular wall tension, wall stress, and myocardial oxygen demand.[11,31] The increase in myocardial oxygen supply is mediated mainly via dilation of epicardial conductance vessels and stenotic sites, relief of coronary artery spasm, dilation of preexisting intercoronary anastomotic channels, decrease in subendocardial compression secondary to decreased left ventricular filling pressure and preload, and an increase in intramural collateral blood flow.[24–26,32]

Since EDRF is decreased in damaged coronary endothelium,[33,34] exogenous nitrate might supply the lacking EDRF and nitrous oxide and produce endothelium-independent vasodilation.[35] This effect is more marked than in the presence of intact endothelium.[35] Since damaged endothelium together with the diminished EDRF and $PGI_2$ promote platelet aggregation, release of vasoconstrictive agents (such as thromboxane $A_2$ and serotonin), and vasospasm,[34] exogenous nitrate can potentially improve coronary perfusion by exerting significant antiplatelet and antithrombotic effects during postinfarction remodeling, maintain patency of the infarct-related vessel after reperfusion therapy, and prevent postinfarction angina and/or recurrent infarction.[36,37] However, a higher dose (1.2 μg/kg/min, or about 70 μg/min) is needed for producing these effects.[37]

It is important to note that the potential for nitrates to increase collateral flow exists whether or not the infarct-related artery is totally occluded. In contrast, the potential for nitrates to increase antegrade flow by their ability to dilate large epicardial vessels and exert spasmolytic, antiplatelet, and antithrombotic effects is limited with total thrombotic occlusions but might be effective in preventing reocclusion, infarct extension, and postinfarction angina after thrombolytic therapy.[38] Since nitrates might dilate coronary veins and lymphatics, they can potentially also improve cellular energetics by increasing coronary venous and lymphatic flow, thereby causing more rapid washout of noxious metabolites of ischemia.[11,39]

**Experimental studies:** Low-dose intravenous nitroglycerin consistently reduced experimental pathologic infarct size.[25,26,40,41] In a conscious dog model, in which pathologic infarct size was measured relative to the size of the occluded bed, or risk region,[25] intravenous nitroglycerin given over the first 6 hours after left circumflex coronary artery ligation in a dose titrated to decrease the mean arterial pressure by 10%, but not <90 mm Hg, resulted in a 54% decrease in left ventricular filling pressure, >50% increase in collateral blood flow, and a 51% decrease in infarct size measured at 2 days (Figure 2). In that study[25] the administration of methoxamine to counteract the small nitroglycerin-induced decrease in blood pressure was associated with similar beneficial effects on infarct size, preload, and collateral flow (Figure 2). These results suggested that the 10% decrease in blood pressure did not contribute significantly to the demonstrated benefits during AMI.

In a similar dog model, but using left anterior descending coronary artery ligation,[26] excessive nitrate-induced hypotension abolished the beneficial effects on collateral flow and infarct size. The paradoxical J-curve effect of progressive nitroglycerin-induced afterload reduction on infarct size is depicted in Figure 3. In this study from our laboratory, infarct size was measured by computerized planimetry 7 days after left anterior descend-

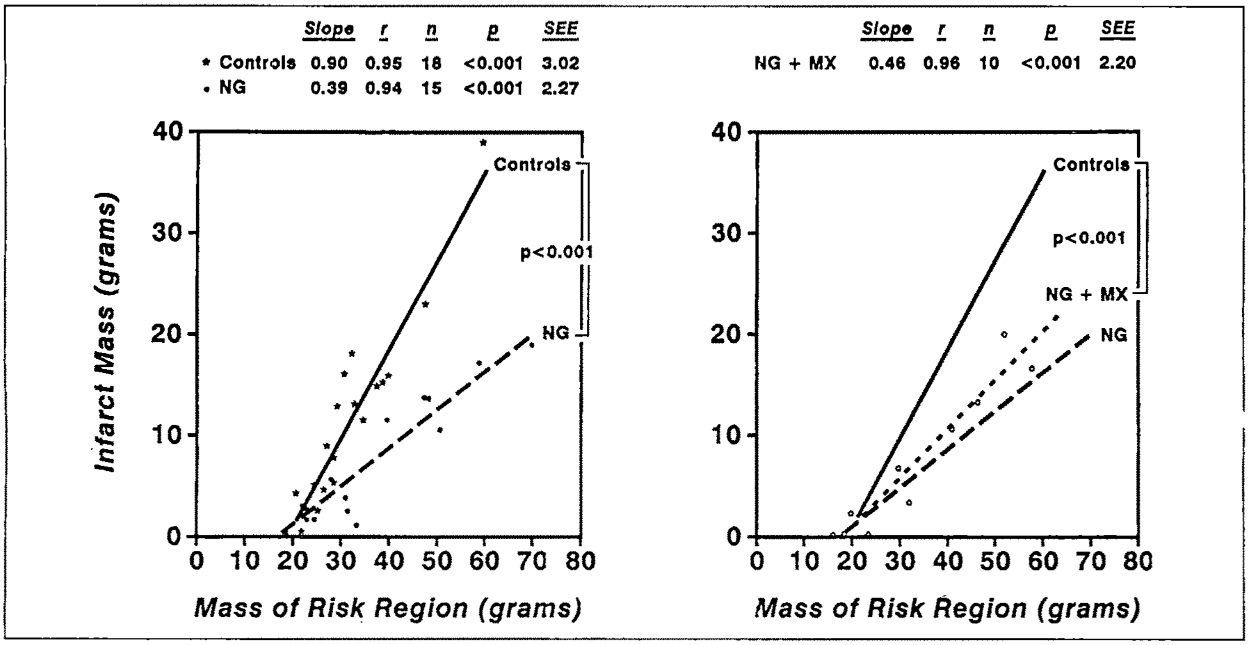

**FIGURE 2. Effect of nitroglycerin *(left)* and nitroglycerin plus methoxamine *(right)* on the relation between myocardial infarct size and the size of the risk region. MX = methoxamine; NG = nitroglycerin; SEE = standard error of the estimate. (Modified with permission from *Circulation*.[25])**

ing coronary artery ligation in the same dog model and expressed as percent of left ventricular mass. The data on 70 dogs that survived 7 days and had similar risk regions (19 saline-treated control dogs; 51 nitroglycerin-treated) indicated that graded reductions in afterload with increasing doses of intravenous nitroglycerin (range 5–300 μg/min) led to more decreases in infarct size, compared with control dogs, for subgroups with decreases in mean arterial pressure in the range from 0 to 20% (down to 78 mm Hg). However, greater decreases in afterload, with mean arterial pressures between 48 and 78 mm Hg, and percent decreases down to 40% led to myocardial underperfusion and increases in infarct size. This underscores the need for caution in administering vasodilators such as nitrates for producing marked decreases of afterload in AMI. In that context, more nitroglycerin is not necessarily better.

**Clinical studies:** The major randomized clinical trials of intravenous nitroglycerin infusions in AMI[14,39,42–47] are summarized in Table I. They all used a low dose but the titration end points differed (Table I). Several studies showed a decrease in ischemic injury,[9,14,39,43,44] reduced creatine kinase infarct size,[14,39,43,46] and smaller perfusion defect scores on thallium scintigraphy.[44] Bussmann et al[48] studied the effect of dose and showed that 3

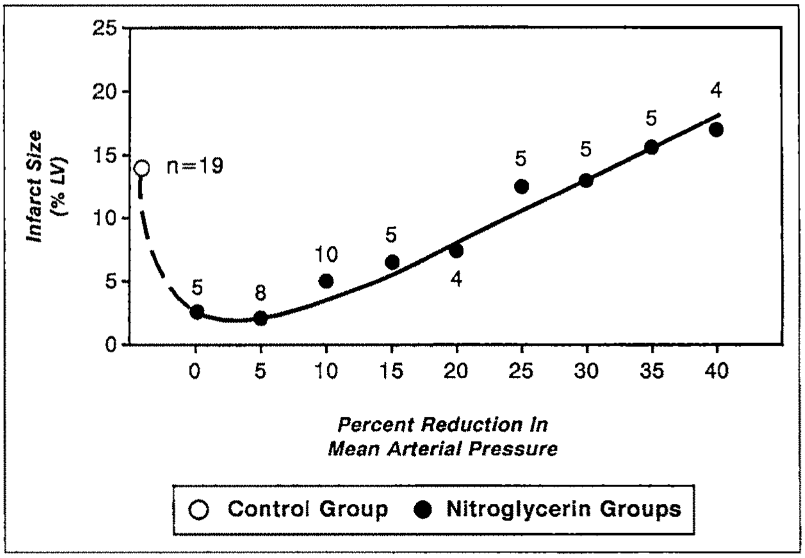

**FIGURE 3. Paradoxical J-curve effect with progressive afterload reduction by nitroglycerin in acute myocardial infarction. LV = left ventricle.**

**TABLE I** Dose and Duration of Intravenous Nitroglycerin in Randomized Trials of Acute Myocardial Infarction

| Reference | Interval from Onset of Symptoms to Therapy | No. of Patients | Duration of Therapy | Dose of Therapy |
|---|---|---|---|---|
| Chiche et al[42] | <24 hr | 35 controls<br>35 NTG | 5–7 days (24 hr for first 12 patients) | Begin 15 μg/min; increased to reduce SBP by 20 mm Hg |
| Bussmann et al[43] | <8 hr (mean 4.5) & >8 hr (mean 12.8 hr) | 29 controls<br>29 NTG | 48 hr | Begin 12.5 μg/min; increased to 100 μg/min to reduce PCWP by 10 to 30% and MBP no more than 10% |
| Flaherty et al[44] | <12 hr | 42 controls<br>56 NTG | 48 hr Intravenous; 24 hr paste (1 inch) | Begin 5 μg/min; increase to reduce MBP by 10%; keep SBP >90 mm Hg, HR >50 bpm |
| Jugdutt et al[39] | <8 hr (mean 5.4) | 11 controls<br>11 NTG | 24–63 hr (mean 39) | Begin 5 μg/min; increased to reduce MBP by 10%, not <80 mm Hg |
| Nelson et al[45] | <14 hr | 14 controls<br>14 ISDN | 90 min | Begin 50 μg/kg/hr, up to 200 μg/kg/hr to reduce MBP by 10 mm Hg |
| Jaffe et al[46] | <12 hr | 42 controls<br>43 NTG | 24 hr (tapered over 4 hr) | Begin 10 μg/min, up to 200 μg/min to reduce SBP by 10% or to 95 mm Hg, not <90 mm Hg; HR not <50 bpm; HR increase not >20 |
| Lis et al[47] | <12 hr | 76 controls<br>64 NTG | 48 hr | Begin 10 μg/min; increased to reduce SBP ≤30 in those with SBP >135 mm Hg, ≤15 in those with SBP 120–134 mm Hg, and ≤5 in those with SBP 95–119 mm Hg (average dose 35 ± 26 μg/min) |
| Jugdutt & Warnica[14] | <12 hr (mean 5 hr) | 156 controls<br>154 NTG | 48 hr (mean 39 hr, range 1–154 hr) | Begin 5 μg/min; increased to decrease MBP by 10% in normotensive and 30% in hypertensive patients but not <80 mm Hg |

bpm = beats per minute; HR = heart rate; ISDN = isosorbide dinitrate; MBP = mean blood pressure; NTG = nitroglycerin; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

mg/hour or 50 μg/min reduced ischemic injury but 6 mg/hour or 100 μg/min produced tachycardia, hypotension, and either less decrease in ST-segment elevation or an increase in ST-segment elevation.

In a large randomized study in which the average dose was only 45 μg/min,[14] the reduction in ischemic injury as well as infarct size (Figure 4) was less in those patients (9% of 154 patients) whose mean blood pressure inadvertently decreased below 80 mm Hg in the first 12 hours. In that study,[14] timing of therapy influenced the degree of myocardial salvage. Thus, the beneficial effect on infarct size was found in patients treated up to 10 hours of

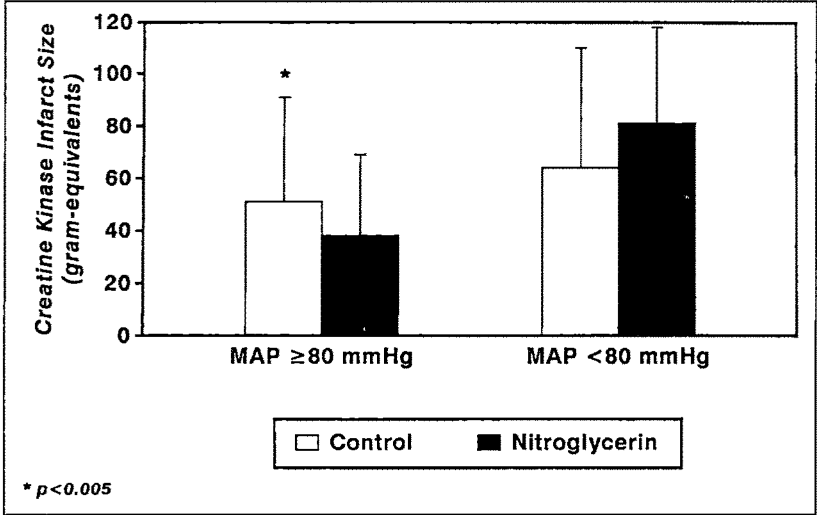

**FIGURE 4. Relation between blood pressure and myocardial salvage during nitroglycerin infusion. MAP = mean arterial pressure. (Modified with permission from *Circulation*.[14])**

onset of pain, but the effect was most marked in those treated early, within 4 hours of onset of pain (Figure 5).

## SALVAGE OF FUNCTION

The first systematic application of intravenous nitroglycerin in AMI was to improve hemodynamics by unloading the left ventricle (Figure 1), predominantly via reduction of preload in patients with elevated left ventricular filling pressure (or preload) using low dose infusions.[6–10] Nitroglycerin, as all nitrates, consistently decreases elevated left ventricular filling pressure. The magnitude of the effect depends on the baseline level, i.e., the higher the baseline filling pressure, the greater the decrease after nitroglycerin.[6] This effect, often referred to as an internal phlebotomy, is due to the venous pooling caused primarily by dilation of systemic and pulmonary veins,[20] although dilation of mesenteric veins[49] and the pulmonary artery[20] might contribute.

Several points need emphasis. First, the favorable effect of intravenous nitroglycerin on hemodynamics in AMI depends on several interrelated factors, some purely hemodynamic (baseline hemodynamic status, degree of hydration and preload; the dose and degree of afterload reduction) and others secondary to effects on myocardial perfusion, ischemic injury, infarct size, and ventricular geometry and remodeling.

Second, the favorable hemodynamic effect is seen at low doses. Bussmann[50] demonstrated that marked and prompt reduction in filling pressure by as much as 40% within 5 minutes was produced by doses that decreased mean arterial pressure by 0–10%. Flaherty et al[6,10] found a 37% reduction of filling pressure with a mean 7% decline in mean arterial pressure. Similar observations were made in several of the randomized clinical trials of low dose nitroglycerin in early AMI.[14,39,42–47] However, in these studies, too, the favorable effect on hemodynamics was partly due to the limitation of ischemic injury,[14,39,43] infarct size,[14,39,43,46] and remodeling.[14]

Third, even with high doses used in patients with congestive heart failure to achieve reduction of left ventricular impedance and afterload as well as preload and to improve left ventricular emptying and ejection, hemodynamics fails to improve in some patients, suggesting resistance.[51,52] Postulated mechanisms for this nitrate resistance include primary receptor resistance, increased vasoconstrictor tone from excess catecholamines, activation of the renin-angiotensin system, hemodilution, edematous vessel walls with impaired ability to dilate, and impaired hepatic metabolism of nitrate.[51,52] Occasionally, marked refractoriness is seen during early uncomplicated AMI, both in dogs[25,26] and patients,[11,13,30,39] when very high doses (>200 μg/min) fail to decrease blood pressure, suggesting primary arterial and arteriolar resistance.[9,10,39]

Fourth, higher doses can be used safely in AMI but it is prudent not to exceed the decremental mean blood pressure cutoff of 80 mm Hg in the first 12 hours.[14] Under special circumstances (e.g., beyond 12 hours of the AMI or more remote AMI when the risk of infarct extension from hypotension is less; presence of hypertension; patients with a lesser risk of infarct extension because the infarct-related artery has been opened by reperfusion therapy), a slightly lower cutoff of mean blood pressure down to 70 mm Hg might be better tolerated, but this has not yet been adequately evaluated. Nevertheless, greater percent reduc-

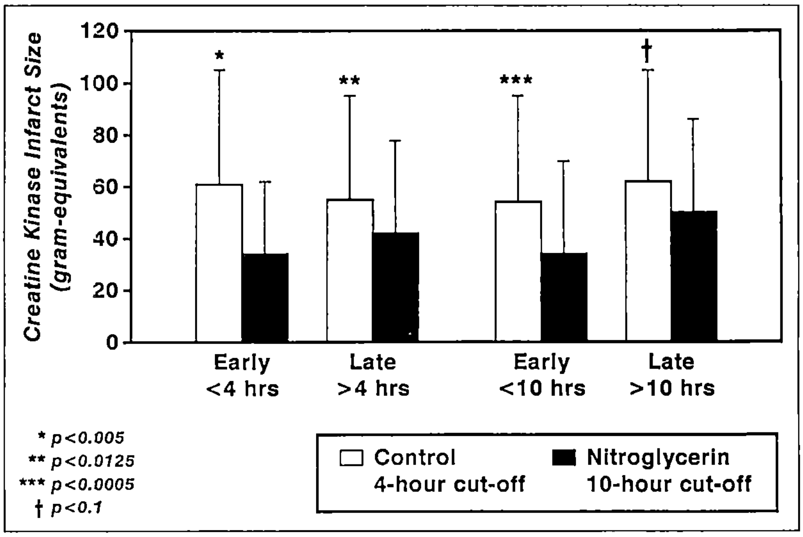

**FIGURE 5. Relation between timing of nitroglycerin therapy and myocardial salvage. (Modified with permission from *Circulation*.[14])**

tions of blood pressure and the additional significant reduction in the patients with hypertension (blood pressure $>140/90$ mm Hg) impacts positively on left ventricular hemodynamics and remodeling.[14]

Fifth, low dose nitroglycerin in AMI consistently produces a leftward and upward shift in the relation between left ventricular stroke volume and filling pressure,[31,39] but stroke output may increase or remain unchanged as preload falls, depending on the baseline value and the shape of the Frank–Starling curve.[31] When afterload is decreased with higher doses of nitroglycerin, stroke output may increase or stay unchanged, but it may also decrease[31,53] if the initial preload is low (as with volume depletion) or the decline in preload is excessive. In the randomized clinical trials with low dose, cardiac output either increased[14,39,43] or was maintained[42,44–47] but did not decrease.

Sixth, the beneficial effects of low dose nitroglycerin on left ventricular unloading, geometry, and infarct size result in decreased regional and global left ventricular mechanical dysfunction[14,39] and improved regional and global ejection fraction.[14,39,44] In the large randomized study of low-dose nitroglycerin by Jugdutt and Warnica,[14] serial 2-dimensional echocardiograms in 128 patients (61 nitroglycerin, 67 placebo) revealed prompt decrease in the total extent of left ventricular akinesis and dyskinesis and improved global ejection fraction (Figure 6). This benefit persisted after acute therapy and was evident at 10 days and 6 months. Furthermore, persistent benefit was found in both anterior and inferior infarction subgroups, was greater in early ($<4$ hours after onset of pain) than late ($>4$ hours) therapy, and less in those with blood pressure $<80$ mm Hg. In the same study,[14] invasive hemodynamic data in 48 patients (19 nitroglycerin, 29 placebo) showed a prompt decrease in pulmonary capillary wedge pressure (20 ± 4 to 14 ± 3 mm Hg; $p < 0.001$) and a late increase in cardiac index (2.7 ± 0.6 vs 3.1 ± 0.5 liters/min/$m^2$; $p < 0.01$) with nitroglycerin but no improvement with placebo.

## SALVAGE OF GEOMETRY

A direct effect of acute left ventricular unloading in AMI (by decreasing preload, afterload, chamber size, and wall stress) is to preserve left ventricular geometry further (Figure 1) by decreasing the magnitude of the mechanical deformation and distension forces acting on the infarct zone and the noninfarcted wall, thereby reducing the outward bulging of the infarct zone and global dilation.[12,13,54] Since early infarct expansion begets more expansion and leads to a vicious cycle of increased wall tension, more infarct stretching and

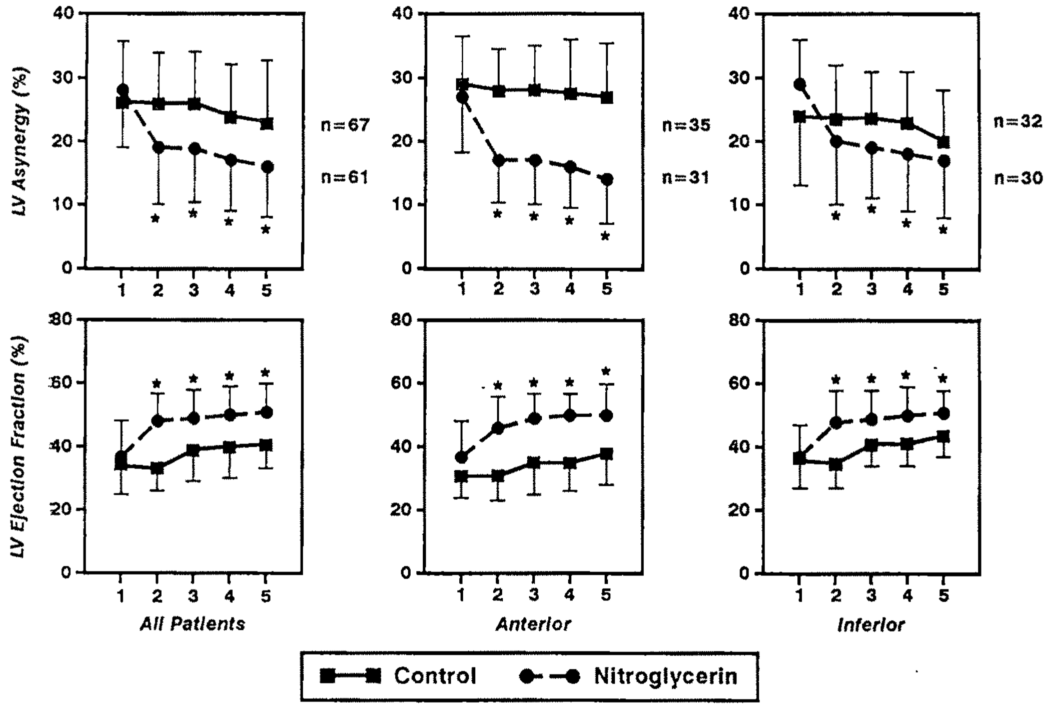

**FIGURE 6. Changes in left ventricular (LV) asynergy and ejection fraction. *p $<0.001$, significance of difference in values at 6 (2), 24 (3), 48 hours (4) and 10 days (5) from baseline value (1) by multiple measures analysis of variance. (Modified with permission from *Circulation*.[14])**

thinning, more global ventricular dilation, aneurysm formation, congestive heart failure, increased risk of cardiac rupture, and increased morbidity and mortality,[12,13,54–58] attenuation of acute expansion by left ventricular unloading can potentially interrupt this cycle. However, a primary determinant of acute infarct expansion is infarct size and transmurality,[12,13,54,57] so that therapy that produces myocardial salvage is an effective means of limiting remodeling.

Experimentally, low-dose intravenous nitroglycerin infusion given for 6 hours after coronary artery ligation results in myocardial salvage and smaller infarcts that are predominantly subendocardial and have greater subepicardial buttressing by normal myocardium at 2 days[25] or 7 days[26] in the dog. In the same dog model, early 6-hour infusion of nitroglycerin also limited infarct thinning and infarct expansion measured at 7 days.[40] Also in the dog model, nitroglycerin given between 2 and 7 days after a left anterior descending coronary artery ligation not only reduced expansion and thinning over 6 weeks, but also improved left ventricular function (as shown by serial echocardiography), improved mechanical strength, decreased distensibility, and increased the rupture threshold.[41]

In clinical studies, low-dose intravenous nitroglycerin over 48 hours persistently decreased left ventricular diastolic and systolic internal dimensions and volumes in anterior[14,39] and inferior[14] AMI for up to 1 year.[14] Limitation of ventricular enlargement was associated with improved ventricular performance in both studies.[14,39] In the larger and more recent study,[14] further evidence of limitation of remodeling was reflected by attenuation of infarct expansion and thinning compared with placebo (Figure 7). In contrast to the placebo group, in which expansion index increased by 31% ($p < 0.001$) and thinning ratio decreased by 17% ($p < 0.001$) at 10 days, these parameters did not change in the nitroglycerin group.[14] More important in that study,[14] limitation of remodeling was also manifested by a decrease in frequency of the clinical infarct expansion syndrome[14,55,57,59] from 15% to 2% ($p < 0.0005$), cardiogenic shock (from 15% to 5%, $p < 0.005$), congestive heart failure, and inhospital mortality from 26% to 14%, ($p < 0.01$). In addition, the functional Killip class score was 40% less by 10 days in the nitroglycerin group compared with placebo.[14]

Although reperfusion attenuates postinfarct remodeling,[60] no full articles have been published during the thrombolytic era to date on the effect on nitroglycerin in AMI. However, several preliminary reports indicate marked benefit with combined nitroglycerin and reperfusion therapy.[61–65] In one study,[61] late reperfusion alone was associated with attenuation of infarct expansion and thinning without improvement of function. However, late reperfusion combined with low-dose nitroglycerin therapy resulted in limitation of remodeling and a prompt improvement in left ventricular function.[61] In the other studies,[62–65] low-dose intravenous nitroglycerin for the first 48 hours, with or without thrombolytic therapy, followed by buccal nitrate for the next 6 weeks resulted in further limitation of remodeling, further improvement in function, limitation of left ventricular dilation, and decreased frequency of aneurysm formation. In these studies,[62–65] an eccentric buccal nitrate dosing schedule was used to avoid tolerance. Also, most patients received thrombolytic therapy with intravenous streptokinase or recombinant tissue type plasminogen activator (rt-PA) concomitantly with low-dose intravenous nitroglycerin infusion, and there was no increased frequency of hypotension.[62–65]

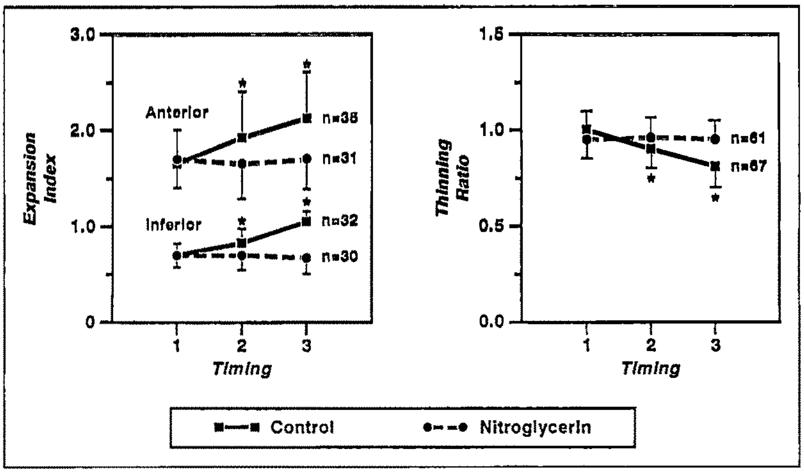

**FIGURE 7. Changes in expansion index *(left)* and thinning ratio *(right)*. *p ≤0.05, significance of difference comparing values at 2–3 days (2) and 10 days (3) from baseline (1). (Modified with permission from *Circulation*.[14])**

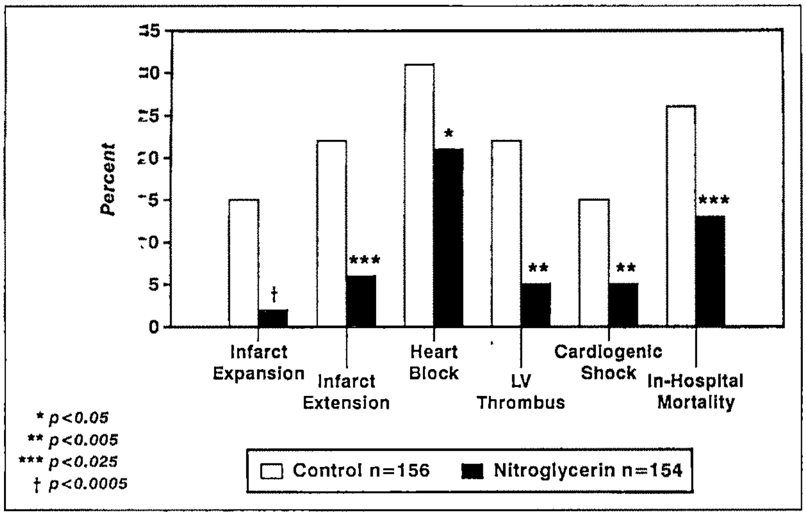

**FIGURE 8. Major inhospital complication rate with nitroglycerin therapy in acute myocardial infarction. LV = left ventricular. (Data from *Circulation.*[14])**

## EFFECT ON OUTCOME AND SURVIVAL

To date, there has not been a large clinical trial of the effect of nitrates on survival in AMI. In the study by Flaherty et al,[44] retrospective analysis revealed that the early subgroup (<10 hours after onset of symptoms) had less infarct complications in the first 10 days, including new congestive heart failure (6% vs 30%), infarct extension (12% vs 26%), and death (4% vs 19%). Total inhospital mortality was also reduced in the early subgroup (15% vs 39%, p = 0.003).

In the study by Jugdutt and Warnica,[14] there was a significant decrease in infarct complications (Figure 8) other than those related to remodeling. Thus, the nitroglycerin group showed less infarct extension (11% vs 22%, p <0.025) and less left ventricular thrombus (5% vs 22%, p <0.005) compared with placebo. In addition, there were fewer deaths inhospital up to 38 days (14% vs 26%, p <0.01), at 3 months (16% vs 28%, p <0.025), and at 12 months (21% vs 31%, p <0.05). However, this effect was mainly seen in the subset of high-risk patients with anterior Q-wave infarction who also had the greatest topographic deterioration (Figure 9). Although lower mortality with low-dose intravenous nitroglycerin was also found in only one other study by Bussmann et al,[43] a meta-analysis of the pooled data from all 8 trials of intravenous nitroglycerin (Figure 10) and oral nitrates conducted by Yusuf et al[15] indicated a 49%

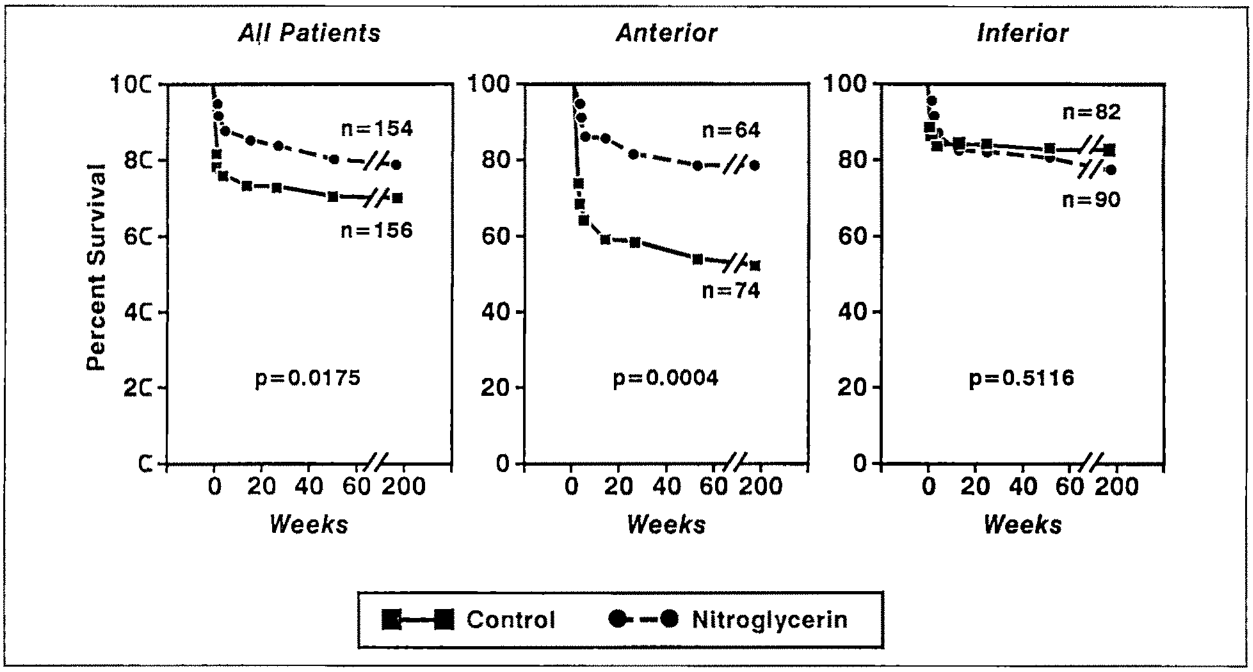

**FIGURE 9. Actuarial survival curves for nitroglycerin and control groups. Data over 43 months or 186 weeks of long-term follow-up are shown. *Left:* all patients. *Middle:* anterior subgroup. *Right:* inferior subgroup. (Data from *Circulation.*[14])**

reduction in the odds of death for all trials with intravenous nitroglycerin (2p <0.001) and a 35% reduction in odds of death (2p <0.001) for all nitrate trials.

## LOW-DOSE REGIMEN

It is clear from experimental and clinical studies that the dosage of nitroglycerin in AMI must be individualized and titrated to a discrete hemodynamic end point. Several arbitrary and elaborate dose titration schedules were used in short-term studies in an effort to avoid nitrate-induced hypotension. Most trials favored a 10% decrease in mean blood pressure as cutoff but never below a mean blood pressure level of 80 mm Hg or a systolic blood pressure level of 90 mm Hg (Table I). It is clear that low-dose nitroglycerin infusion can be given safely during AMI to modify multiple biologic and clinical end points favorably.[14,39,42–47] Blood pressure can be monitored noninvasively,[14,44] using a standard sphygmomanometer,[14] and can be done by the nursing staff.[11] To allow for the variability in blood pressure in early AMI, mean blood pressure cutoffs of 10% for normotensive patients and 30% for hypertensive patients (defined as blood pressure >140/90 mm Hg) was used effectively by Jugdutt and Warnica.[14] The low-dose regimen used by my group (Table II) is similar to that recommended by the task forces of the American College of Cardiology and the American Heart Association in 1990.[66] Nitroglycerin for intravenous use is commercially available in North America but can be prepared by the hospital pharmacy. The infusion is begun at 5 μg/min, titrated upward to the target level, and generally maintained for 48 hours unless excessive hypotension develops. Mean blood pressure is calculated as two thirds diastolic plus one third systolic blood pressure. There is no safe fixed dose. Nitrate resistance and tolerance require upward titration. However, partial tolerance, seen after a mean of 11 hours in 24% of patients who required increase in dose to maintain the desired hemodynamic effect, only blunted the beneficial effect on infarct size and did not affect beneficial effects on function, topography, and complications.[14,30] Greater caution should be exercised in patients prone to increased nitrate sensitivity, e.g., hypovolemia; inferior AMI; the right ventricular infarction syndrome; the elderly. Blood pressure, heart rate and clinical status are monitored during the infusions.

**TABLE II** Typical Protocol for Low Dose Intravenous Nitroglycerin

1. Can use standard intravenous set with infusion pump
2. Begin at 5 μg/min; increase by 5–10 μg/min every 5–10 min until the desired end point or a dose of 200 μg/min is reached
3. Titrate to desired hemodynamic end point: lower mean BP by
    - 10% in normotensives
    - 30% in hypertensives
    - but not <80 mm Hg
4. Reassess if:
    - systolic BP <90 mm Hg
    - mean BP <80 mm Hg
    - diastolic BP increases >15 mm Hg
    - heart rate increases >20% or decreases <50 bpm
5. Continue infusion for at least 24 hours, preferably 48 hours
6. Discontinue if hypotension; restart at 5 μg/min when safe
7. To stop, titrate down by 5–10 μg/min every 5–10 min
8. Average dose range 30 to 140 μg/min

BP = blood pressure; bpm = beats per minute.

In conclusion, left ventricular unloading with low dose intravenous nitroglycerin infusion can be safely applied to salvage ischemic myocardium, geometry and function after AMI and improve outcome and survival.

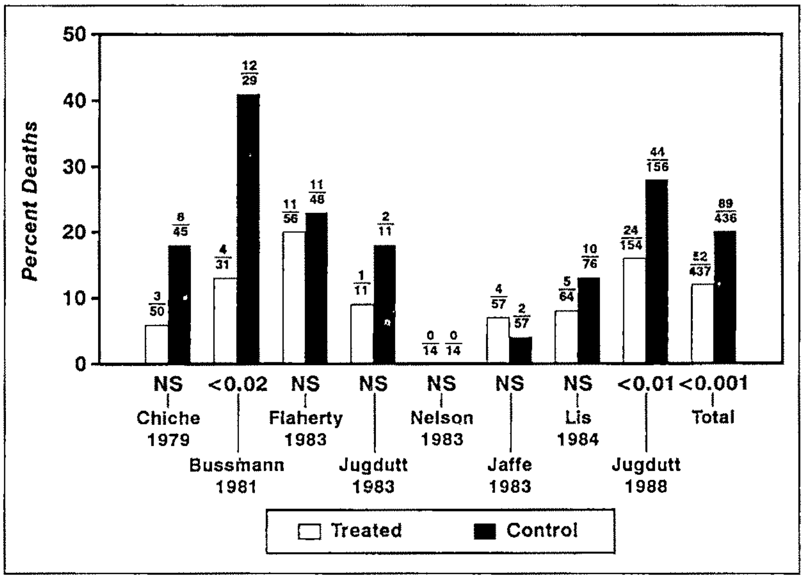

**FIGURE 10. Mortality in randomized trials of intravenous nitroglycerin. NS = not significant.**

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# Early Preventive Treatment of Left Ventricular Dysfunction Following Myocardial Infarction: Optimal Timing and Patient Selection

Norman Sharpe, MD

**Treatment for clinical congestive heart failure is effective, but because severe ventricular dysfunction is often present at the time of clinical presentation, it may only be palliative. Recent clinical studies indicate that treatment of symptomless left ventricular dysfunction from 1 week following myocardial infarction or later may prevent further ventricular dilation and possibly reduce the occurrence of heart failure. Considering the potential for progressive ventricular dilation that exists from the time of myocardial infarction, early intervention following myocardial infarction may provide greater benefit. In a double-blind study, 100 patients with Q-wave myocardial infarction, but without clinical heart failure, were randomized to treatment with captopril 50 mg twice daily or placebo, 24–48 hours following onset of symptoms. During 3 months of treatment, the placebo group showed significant increases in left ventricular end-diastolic and end-systolic volume indices with ejection fraction unchanged. In contrast, the captopril group showed a slight but insignificant increase in left ventricular end-diastolic volume index and a significant reduction in end-systolic volume index with ejection fraction increased. Thus, early treatment of patients following Q-wave myocardial infarction with converting enzyme inhibition is effective in preventing ventricular dilation and provides an advantage over later treatment. Selection of patients with Q-wave infarction at 24 hours, after thrombolysis, provides therapy for those most likely to benefit, which is well tolerated without risk of hypotension.**

**(Am J Cardiol 1991;68:64D–69D)**

The rationale for treatment of symptomless left ventricular dysfunction is based on the known poor prognosis for heart failure and the fact that severe left ventricular dysfunction is often present by the time overt congestive heart failure is manifested clinically. Evolution of Q-wave infarction may be followed by early infarct expansion[1] and later by progressive global ventricular dilation[2] (Figure 1). Ventricular volumes are strong predictors of long-term survival[3] and congestive heart failure occurs increasingly during the years following myocardial infarction.[4] Intervention to prevent heart failure may be considered at various stages following myocardial infarction with different processes amenable to treatment at different times (Figure 2).

Recent clinical studies have demonstrated that angiotensin–converting enzyme (ACE) inhibition can improve symptomless left ventricular dysfunction and possibly prevent congestive heart failure when treatment is commenced 1 week following myocardial infarction or later.[5–7] Also partial reversal of progressive left ventricular dysfunction can be achieved with treatment after 1 year.[8] However, ventricular dilation can occur from the time of myocardial infarction, and early intervention, rather than from 1 week or later, may provide greater benefit. Immediate treatment, from the time of admission may confer maximal benefit but will be nonselective and possibly difficult to administer with concomitant thrombolysis. Treatment of patients with Q-wave infarction after 24 hours may be more practical because it will provide therapy to those most likely to benefit. Thus, we studied the effects on ventricular size and function of ACE inhibition commenced 24–48 hours following the onset of symptoms in patients with Q-wave myocardial infarction.[9]

## PREVENTIVE TREATMENT

Patients with definite Q-wave myocardial infarction who were clinically stable 24–48 hours following the onset of symptoms were considered for the

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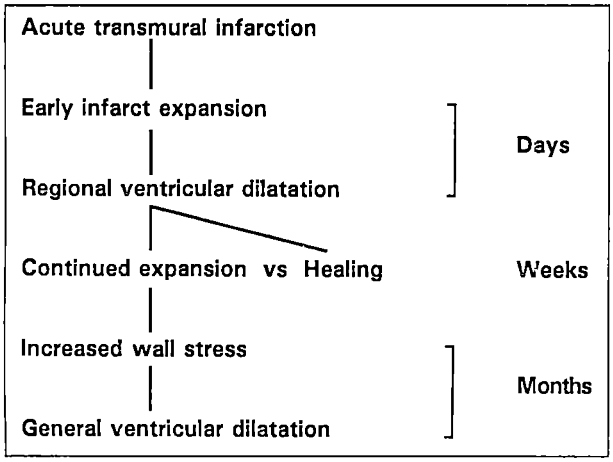
Acute transmural infarction
Early infarct expansion
Regional ventricular dilatation
Days
Continued expansion vs Healing
Weeks
Increased wall stress
General ventricular dilatation
Months

**FIGURE 1. Ventricular dilation following myocardial infarction.**

study. Those who had received thrombolysis following admission were considered for inclusion providing evolution of Q waves was evident electrocardiographically. Eligible patients underwent 2-dimensional echocardiography and those with adequate image quality who provided informed consent and tolerated an open test dose of captopril 12.5 mg were randomized. Patients received double-blind treatment with either captopril or placebo. Captopril 25 mg twice daily or placebo was given on the first day, increasing to 50 mg twice daily on the second day and continuing on this dose for 3 months. In cases of significant hypotension (systolic blood pressure <80 mm Hg or occurrence of symptoms), dosage was reduced and later increased according to blood pressure. Patients were reviewed with clinical and echocardiographic assessment at 1 week, 1 month, and 3 months and finally after a 48-hour treatment withdrawal period. Clinical congestive heart failure occurring during the trial period was treated with furosemide and patients not controlled with diuretic treatment were withdrawn from the trial for open treatment. Patients with angina not responding to nitrates and β blockers and requiring coronary angiography were withdrawn, as were those with reinfarction. The end points of the study were left ventricular volumes and function measured by 2-dimensional echocardiography and the occurrence of clinical heart failure requiring diuretic treatment or trial withdrawal. Echocardiographic methods of examination, analysis, and normal values have been previously described.[5] Left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and stroke volume index (SVI) were estimated at each assessment.

One hundred patients were randomized to treatment with captopril or placebo following assessment of 114 patients with Q-wave infarction, 12 of whom were excluded because of inadequate echocardiographic image quality and 2 because of symptomatic hypotension following test dosage with captopril. The clinical characteristics of the 2 treatment groups were similar, with a predominance of male patients, approximately equal numbers of patients with anterior and inferior myocardial infarction, and with 72% of all patients having had thrombolytic treatment. Baseline echocardiographic measurements of left ventricular volumes and function are shown in Table I and Figure 3.

The treatment effect observed between the groups for the changes in left ventricular volumes was significant (LVEDVI and LVESVI both $p < 0.0001$). The unadjusted volume data at baseline and 3 months are shown in Figure 4. The adjusted mean differences from baseline are shown in Figures 5 and 6. The placebo group showed significant increases in LVEDVI and LVESVI from 1 week to 3 months, with SVI increased and ejection fraction unchanged. In contrast, the captopril group showed no significant change in LVEDVI and a significant reduction in LVESVI from 1 week to 3 months, resulting in significant increases in

**FIGURE 2. Earlier intervention in heart failure.**

| PROCESS | | AIM |
|---|---|---|
| Coronary occlusion | - | Restore patency |
| Myocardial infarction evolving | - | Optimise $O_2$ supply:demand |
| Myocardial infarct expansion | - | Reduce regional wall stress |
| Ventricular dilation and remodeling | - | Reduce wall stress and hypertrophy |
| Ischaemia<br>Recurrent infarction<br>Arrhythmias | - | Optimise $O_2$ supply:demand |
| Congestive heart failure | - | Relieve congestion<br>Block neurohormonal activation<br>Improve contractility |

**TABLE I** Baseline Echocardiographic Measurements of Left Ventricular Volume

| Left Ventricular Volume Indices | Captopril Group (n = 50) | Placebo Group (n = 50) | Normal Values (n = 50) |
|---|---|---|---|
| LVEDVI (mL/m²) | 73.3 (16.5)* | 68.4 (18.2)* | 56.2 (9.0) |
| LVESVI (mL/m²) | 44.2 (12.2)* | 40.4 (13.1)* | 25.7 (5.0) |
| Stroke volume index (mL/m²) | 29.1 (7.4) | 27.9 (7.5) | 30.5 (5.3) |
| Ejection fraction (%) | 40.2 (7.0)* | 41.1 (6.4)* | 54.4 (3.4) |

*p <0.0001 vs normal values.
Values are mean (standard deviation).
LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index.

SVI and ejection fraction. Most of the treatment benefit was evident within the first month, and at 3 months there was a 4.6% difference (p <0.0001) in the change in ejection fraction from baseline between the 2 groups. There was no change in left ventricular volumes following the 48-hour treatment withdrawal period after 3 months. During the study period 7 patients in the captopril group and 7 in the placebo group were treated with furosemide. Three of these, 1 in the captopril group and 2 in the placebo group, were withdrawn from the study with severe heart failure requiring open-label treatment. Anterior and inferior infarct subgroups showed similar changes in left ventricular volumes and function (Figure 7). There was no different treatment effect observed in the minority (28%) of patients who did not receive thrombolysis for any of the dependent variables.

## TIMING OF INTERVENTION AND PATIENT SELECTION

It is clinically important to consider the optimal timing of this treatment following myocardial infarction. Recent experimental studies in rats with myocardial infarction have demonstrated a beneficial effect of captopril on left ventricular performance, weight, and volume,[10] which is consistent with the results of previous similar studies.[11] However, there was no difference in the benefit with immediate treatment commenced orally 2 hours after coronary ligation compared with delayed treatment initiated at 21 days when the animals were studied after 4 months of treatment.[10] However, although immediate parenteral rather than oral treatment may have been more effective, it is also possible that immediate treatment may confer some disadvantages, which tend to reduce the overall benefit of treatment. Blockade of compensatory mechanisms activated at the time of infarction may not be desirable in the immediate postinfarction period, even though these mechanisms may be deleterious later. Also, while the rat model is useful for studies of left ventricular remodeling after myocardial infarction, patients with coronary artery disease may respond differently to ACE inhibition.

In contrast to the animal data, comparison of this early intervention study and previous clinical studies does indicate that early treatment provides a greater benefit. In our previous clinical study[5,7] we selected patients with Q-wave infarction for treatment with captopril at 8–9 days following myocardial infarction and continuing for 1 year. At baseline, mean LVEDVI was approximately 35% above normal and LVESVI approximately 85% above normal (compared with approximate increases in LVEDVI and LVESVI of 25% and 50%, respectively, at 24–48 hours in the early intervention study). Although captopril significantly reduced ventricular dilation in contrast to the further dilation that occurred with placebo, after 1 year of captopril treatment LVEDVI was still 30% increased and LVESVI still 50% increased. Mean ejection fraction had improved from approximately 37% to 44%. Thus, despite a beneficial effect from captopril treatment, most patients still had moderate left ventricular dilation and dysfunction persisting. In a further study,[8] a group of patients who had demonstrated progressive ventricular dilation during the first year following myocardial infarction

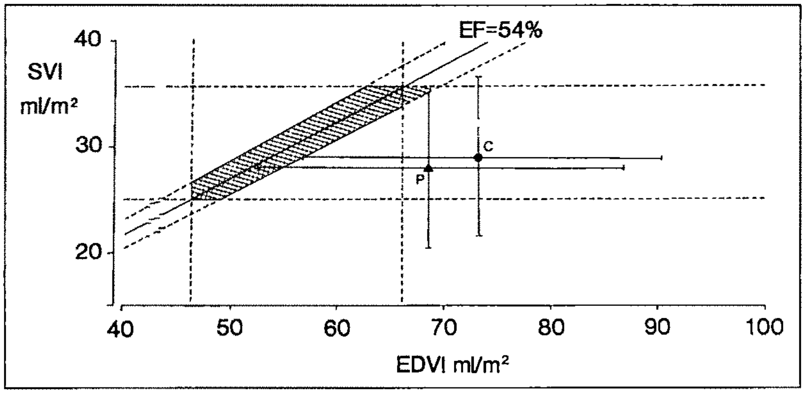

**FIGURE 3. Baseline values for stroke volume index (SVI) and left ventricular end-diastolic volume index (EDVI) for the captopril (C) and placebo (P) groups. The dotted lines enclose the normal range for these volumes and the shaded area the normal range for ejection fraction (EF) (mean ± standard deviation).**

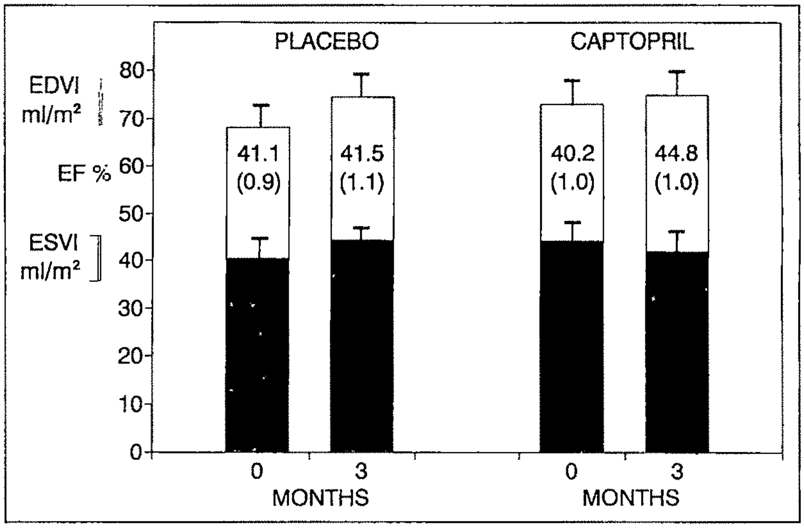

**FIGURE 4. Unadjusted left ventricular volume data for treatment groups at baseline and 3 months. Numbers in columns refer to mean (standard error [SE]) ejection fraction (EF) (%). Vertical bars represent SE. EDVI = end-diastolic volume index; ESVI = end-systolic volume index.**

were treated openly with captopril during the second year. Although partial late reversal of left ventricular dilation was achieved during the second year, the group did not achieve restoration to their baseline left ventricular function assessed 1 week following myocardial infarction.

Patients in the early intervention study had very similar baseline characteristics to those in our previous study,[5,7] although there were more anterior infarcts in that study. Ventricular dilation, as expected, was less 24–48 hours following myocardial infarction than at 1 week, but after 3 months, ventricular volumes in the placebo groups from the 2 studies were similar. In assessing the benefit of early administration of captopril, comparison of the 2 studies shows that earlier treatment not only prevented the substantial ventricular dilation evident at the time of entry in our previous study 1 week postinfarction, and at 1 week in the placebo group in the early intervention study, but also improved ventricular function significantly from the earlier baseline. Thus, captopril treatment

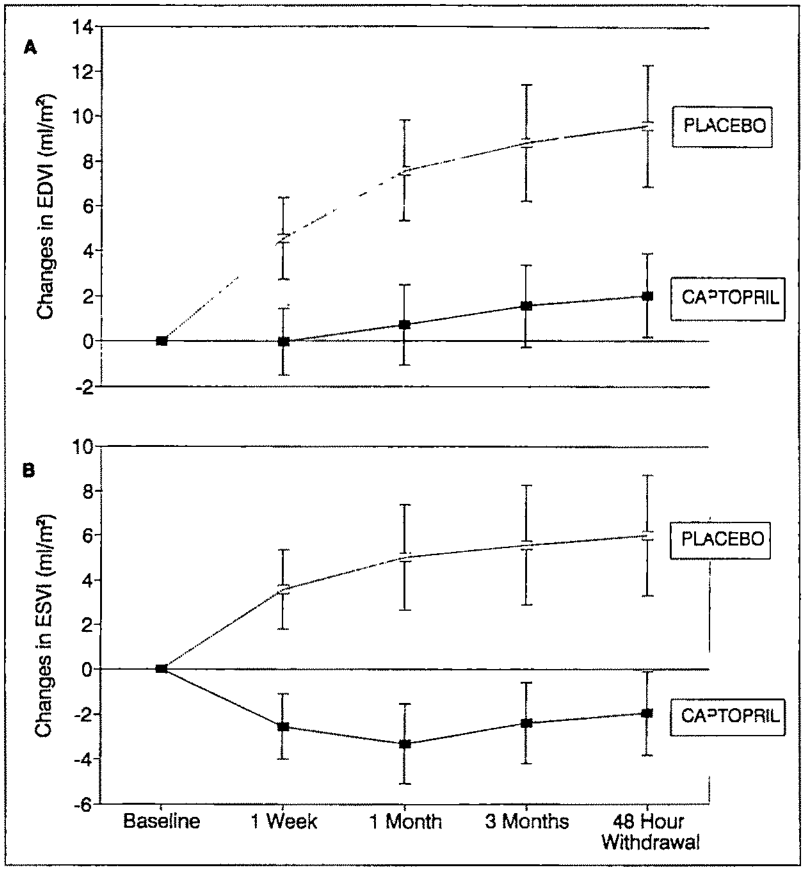

**FIGURE 5. Adjusted mean differences from baseline at 1 week, 1 and 3 months and after 48 hours withdrawal for the treatment groups for left ventricular end-diastolic volume index (EDVI; *A*) and left ventricular end-systolic volume index (ESVI; *B*). Values shown are means with 95% confidence intervals.**

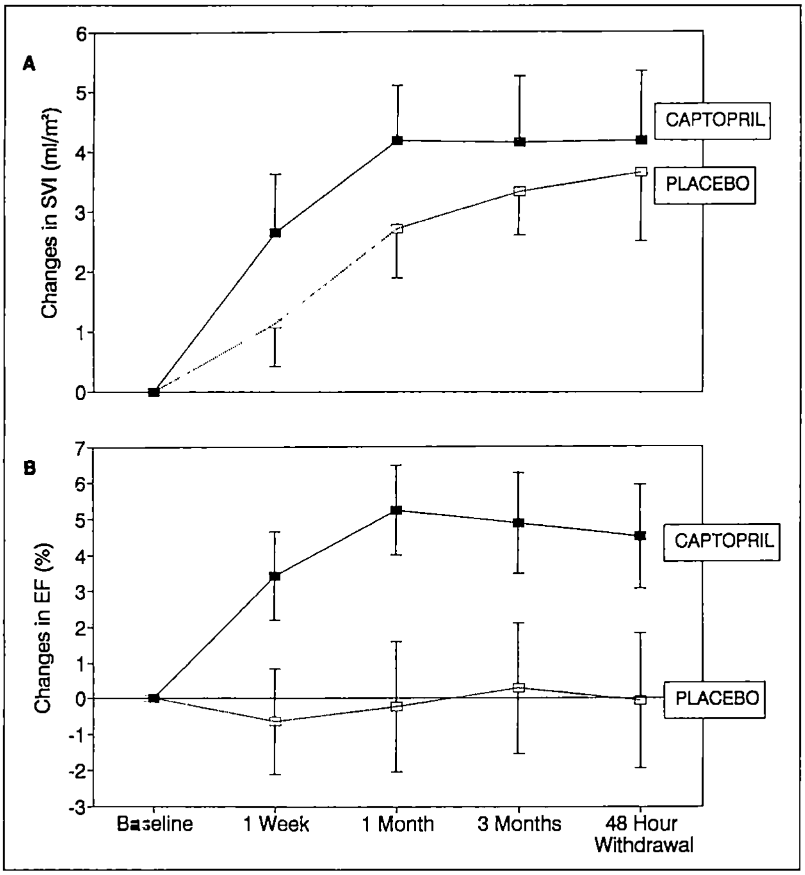

**FIGURE 6. Adjusted mean differences from baseline at 1 week, 1 and 3 months and after 48 hours withdrawal for the treatment groups for stroke volume index (SVI; *A*) and ejection fraction (EF; *B*). Values shown are means with 95% confidence intervals.**

24–48 hours following infarction appears feasible and provides a definite advantage over later treatment.

The comparative theoretical advantages and disadvantages of immediate, early and delayed intervention with converting enzyme inhibition following myocardial infarction are shown in Figure 8. A generalized nonselective treatment approach at the time of admission can be compared with a more selective early or delayed strategy based on the identification of patients with Q-wave infarction or significant left ventricular dilation and dysfunction. Following the initial phase of myocardial infarct evolution and as ventricular remodeling progresses, the peripheral vasodilating effect of captopril is probably the predominant mechanism of improvement and in this respect preload and afterload reduction appear important.[12] Captopril may have a beneficial effect on the coronary circulation[13,14] and also direct effects on

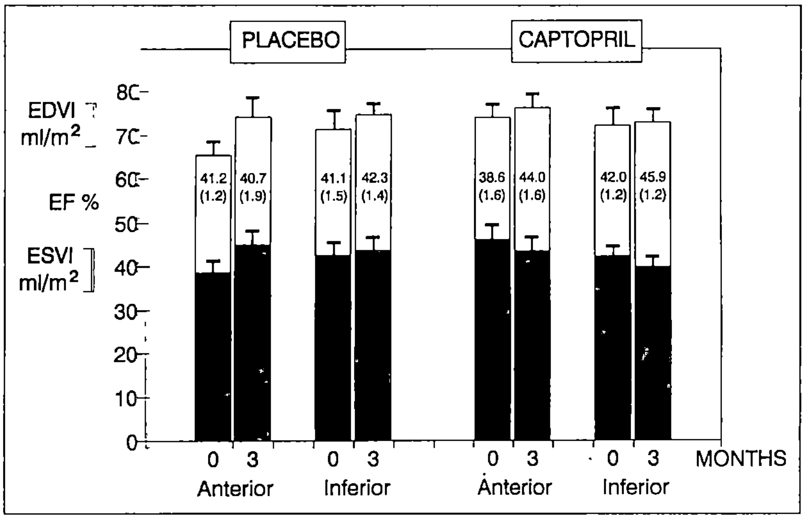

**FIGURE 7. Left ventricular end-diastolic and end-systolic volume index (EDVI, ESVI) data for anterior and inferior infarct subgroups at baseline and 3 months. Numbers in columns refer to mean (standard error [SE]) ejection fraction (EF) (%). Vertical bars represent SE.**

**FIGURE 8. Timing of intervention with angiotensin-converting enzyme inhibition following myocardial infarction (MI). LV = left ventricular.**

| BENEFIT | RISK |
|---|---|
| IMMEDIATE (Admission) Non selective | |
| - Infarct size reduced | - Blockade beneficial compensatory mechanisms? |
| - Reperfusion injury attenuated | - Hypotension |
| - Infarct expansion prevented | |
| EARLY (Days) Q wave MI | |
| - Infarct expansion reduced | - Ventricular dilation and dysfunction progressive |
| - Ventricular dilation and hypertrophy prevented | - Prognosis worsening |
| - Myocardial ischaemia reduced | |
| DELAYED (Weeks-Months) LV dilation - dysfunction | |
| - Ventricular dilation and dysfunction improved | - Ventricular dysfunction only partially reversible |
| - Heart failure prevented? | - Prognosis poor - related to ventricular dilation |
| - Survival improved? | |

myocardial tissue,[15,16] which are advantageous for long-term remodeling.

## FUTURE STUDIES

While we have shown that early treatment of patients following myocardial infarction with ACE inhibition is feasible and provides an important ventricular function benefit during the first 3 months, ideally further clinical studies are required with randomization at different times after myocardial infarction to confirm the optimal timing of treatment. Similar treatment in combination with, or immediately after, thrombolysis is currently being assessed in other studies. Assessment of the comparative and possibly additive effects of ACE inhibition, nitrates, and β blockers in the postinfarction period is also required. The results of larger studies are awaited to indicate the benefit of this type of treatment in terms of long-term heart failure prevention and survival.

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# Rationale, Design and Baseline Characteristics of the Survival and Ventricular Enlargement Trial

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**Heart failure, often associated with ventricular enlargement and recurrent myocardial infarction, is one of the major causes of postinfarction mortality. This observation suggests that measures used to prevent ventricular enlargement may improve postinfarction survival. The Survival and Ventricular Enlargement (SAVE) trial is a randomized, double-blind, placebo-controlled clinical trial with the purpose of evaluating the effect of angiotensin-converting enzyme (ACE) inhibition on postinfarction death and ventricular dilation. This multicenter trial had a sample size goal of 2,220 patients between 21 and 79 years of age who had recently sustained a myocardial infarction and who have an ejection fraction determined by radionuclide ventriculogram (RVG-EF) of ≤40%. In addition to conventional therapy, patients were randomly assigned to captopril or placebo therapy commencing within 3–16 days following their myocardial infarction. A second RVG-EF is performed on all surviving participants at the end of the average 3.5-year treatment and follow-up period. The study has 90% power to detect a 25% improvement in postinfarction mortality or prevention of ≥9 unit absolute reduction in radionuclide ejection fraction. Additional end points, design features, and the administrative organization of the trial are described.**

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Survivors of myocardial infarction (MI) are at heightened risk for subsequent cardiovascular events, heart failure, recurrent MI and death. This risk can vary considerably and is a complex function of the severity of myocardial dysfunction, the severity of underlying coronary artery disease, the arrhythmia profile, the presence of concomitant disease and age. These factors all interact as determinants of clinical outcomes following MI. The degree of left ventricular dysfunction is often assessed by global ejection fraction, which is a major—perhaps the most important—determinant of most risk factor stratifications.[1-3] Although left ventricular ejection fraction is an extremely powerful predictor of adverse outcome, quantitative measurements of left ventricular volume have provided even further discrimination with respect to postinfarction survival.[4] The process of ventricular enlargement can be detected in the early phases of MI by the echocardiograph as infarct expansion, a process characterized by elongation and thinning of the infarct-containing segment.[5,6] However, lengthening of the noninfarct zone also contributes to the overall increase in ventricular size.[7,8] The eventual volume of the infarcted ventricle has been shown to be related to the size of the infarct as assessed by the proportion of the ventricular silhouette, which is either akinetic or dyskinetic.[8-10] Patients manifesting this process are at heightened risk for the development of aneurysms, congestive heart failure, and fatal events. However, patients demonstrating early infarct expansion are also at risk for progressive and global ventricular enlargement.

Recent animal and clinical studies have demonstrated that the ventricular dilation that occurs following MI is related to the extent of myocardial damage[11] and that this enlargement, once present, may be progressive.[12] A cycle of progressive dilation leading to further increases in systolic and diastolic wall stress, which in turn results in progressive left ventricular enlargement and dysfunction has been formulated. This pathophysiologic con-

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struct provided the basis for the initial animal studies in which the angiotensin-converting enzyme (ACE) inhibitor captopril was administered chronically to rats following experimental infarctions in an attempt to reduce wall stress and attenuate ventricular enlargement following experimental MI. This progressive increase in ventricular chamber size was, indeed, attenuated in this experimental model.[13] When continued for up to 1 year, ACE inhibition both diminished the tendency to left ventricular enlargement and prolonged the survival of animals with experimental infarction.[14] It was shown that this reduction in left ventricular volume enlargement was a consequence of both reduced filling pressure (distension) and structural remodeling, i.e., a shift to the right of the pressure–volume curve with an increase in ventricular volume at any distension pressure. These initial studies confirmed that, for comparable degrees of histologically determined infarct size, this chronic administration of an ACE inhibitor is associated with smaller ventricular volumes and improved survival in an animal model.

Applicability of these animal studies to patients was supported by trials specifically designed to determine which ACE inhibitor therapy would favorably alter the process of ventricular enlargement following MI.[15,16] Since the specific end point of each of these trials was ventricular size, these trials were not designed with sufficient statistical power to address clinical events. Given the importance of ventricular enlargement and function on the overall prognosis following MI, an hypothesis that ACE inhibition therapy would be effective in improving survival and reducing left ventricular dysfunction and cardiovascular morbidity in myocardial infarct survivors with left ventricular dysfunction was constructed.

**TABLE I** SAVE Major Inclusion and Exclusion Criteria

- Inclusion
  - Men and women 21 to 79 years of age
  - Confirmed acute myocardial infarction between 3 and 16 days preceding randomization
  - Radionuclide left ventricular ejection of $\leq 40\%$
- Exclusion
  - Women of childbearing potential unless contraception is used
  - Patients with contraindication to captopril
  - Patients with congestive heart failure despite treatment with digitalis and diuretics who require vasodilator therapy prior to randomization
  - Patients with any of the following
    - Serum creatinine $>2.5$ mg/dl
    - Malignancy thought to reduce survival or requiring radiation therapy
    - Hypertension requiring vasodilator therapy at the time of screening
    - Severe valvular heart disease likely to require a surgical procedure
    - Other conditions thought to limit survival
    - Psychologic disorder making the patient unsuitable for a clinical trial
    - Participation in another investigational drug trial
    - Clinical ischemia with no corrective procedure
    - Prior to the scheduled time of randomization
    - Ischemia or hypotension following the test done of captopril
    - Unwilling to consent

## OBJECTIVES, DESIGN, AND ORGANIZATION

**Objectives:** The primary objective of the SAVE trial is to assess whether treatment with captopril will improve survival without marked deterioration of left ventricular performance of patients who have recovered from an acute MI. The prospectively specified, primary study end point is a combined measure of mortality and survival with $\geq 9\%$ reduction in left ventricular ejection fraction. The secondary end points of SAVE are to evaluate the effects of captopril on total mortality; cardiovascular mortality and cause-specific mortality; frequency of decline in left ventricular function as measured by radionuclide angiography; development of congestive heart failure, severe enough to clinically require open-label ACE inhibition; survival without the development of heart failure severe enough to require open-label ACE inhibition; survival without the development of recurrent MI; survival without the development of either MI or a serious deterioration of left ventricular function; survival without the development of either MI or heart failure severe enough to require open-label ACE inhibition; survival without the development of either MI or heart failure severe enough to require open-label ACE inhibition or a serious deterioration of left ventricular function; hospitalization requirement for congestive heart failure; and hospitalization requirement for cardiovascular events. The SAVE study is also evaluating the possible adverse effects of chronic captopril therapy. In the placebo cohort, the time-dependent development of symptomatic heart failure requiring adjustments to diuretics or digitalis therapy and in more refractory cases, open-label ACE inhibition will be examined.

**Design:** SAVE is a multicenter, double-blind, placebo-controlled clinical trial conducted in 45 centers in the United States and Canada. Men and women aged 21–79 who recently sustained a MI with resultant left ventricular ejection fractions $\leq 40\%$ have been recruited into 1 of 2 treatment arms within 3–16 days of the index MI. Inclusion and exclusion criteria are as listed in Table I. These patients are being followed for an average of 3.5 years (minimum 2-year follow-up).

The change in radionuclide ventricular ejection fraction (RVG-EF) chosen as a component of the primary end point of SAVE was selected as an objective measure that is anticipated to occur infrequently but, when present, is deemed to be of major clinical significance. Before any final RVG-EF examinations were obtained, an exploratory analysis was undertaken of the baseline RVG-EF studies to determine the variability of the RVG-EF measurement. The reproducibility of the RVG-EF was obtained by determining the standard deviation of the difference (interpretation 1 vs 2) of >200 baseline RVG-EFs taken at this center. This measurement suggested that a change of 9 percentage points in the RVG-EF would signify a decrease in RVG-EF, which was unlikely to be due to chance alone. In addition, observations of repeat RVG-EF determinations confirmed that patients with ejection fraction deteriorations ≥9% were experiencing an increased risk of death, making this magnitude of deterioration clinically relevant. Thus, the occurrence of this uncommon RVG-EF event, which was evidence of marked deterioration in left ventricular function, was likely to be of clinical importance with a longer duration of patient follow-up. After review of this interim data but before any terminal RVG-EFs were obtained at the study's end, the decision was made to set the minimum change in RVG-EF as a deterioration of ≥9 units for the component of the primary end point in a patient surviving to the end of the trial.

A goal of 2,220 randomized participants was accepted as the recruitment goal for SAVE. This number was based on the following assumptions as to the size of the sample:

1. The primary end point is either death from any cause or survival and a ≥9 unit reduction in ejection fraction as determined by RVG-EF.
2. The average follow-up time for patients in the study is 3.5 years.
3. The efficacy, uncorrected for patients who change therapy group, is 25%.
4. The cumulative mortality rate for the SAVE placebo group is 20%.
5. The overall percentage of surviving patients experiencing a reduction (in ejection fraction) of ≥9 units is 9% in the placebo group.
6. The projected yearly dropout rate for patients who are initially assigned to active therapy but in whom the active medication is discontinued is 17% the first year, 9% the second year, and 7% the third year
7. The projected yearly drop-in rate for patients who are initially assigned to placebo therapy but go on active open-label therapy is 9% for the first year, 7% for the second year, and 5% for the third year.
8. In a 2-tailed test of significance, the maximum type I error is 0.05, and the power for a statistical test on the primary end point of SAVE is 90%.

*Treatment program:* SAVE participants were randomized in equal numbers and in a double-blind manner to either captopril or placebo. The randomization process was stratified by age (>70 years) and ejection fraction (<20%), guaranteeing that the small subset of patients at the highest risk for reduced survival were allocated evenly between therapy groups. In addition, randomization was also stratified for participating centers.

Prior to randomization, all eligible and consenting patients were given a test dose of open-label captopril 6.25 mg orally. If this initial dose was well tolerated and not associated with significant orthostatic or ischemic symptoms, the patient was randomized to receive either captopril or placebo therapy in a double-blind fashion. The initial dose of blinded study drug was 12.5 mg. However, in patients with marked but asymptomatic reduction in pressure with the initial test dose, the patient was allowed to receive 6.25 mg of the blinded therapy as the initial postrandomization dose. The study medication was then advanced as tolerated to a maximum of 50 mg 3 times daily.

Patients were first scheduled for follow-up examinations 2 weeks after randomization. Subsequent follow-up visits are every 3 months during the first year and every 4 months thereafter. At each visit, a history and physical examination, including functional capacity, are obtained. Interim clinical events since the last visit are elicited and recorded on study forms. In addition, possible adverse reactions are recorded. The evaluation of compliance to medication is ascertained through the use of pill counts.

Although physicians are encouraged to use other therapy modalities for the treatment of congestive heart failure, they had the option of using open-label captopril for patients not responding to conventional therapy. When this option was chosen, the Clinical Coordinating Center was notified and confirmed that the treating physician believed the patient required ACE inhibition for congestive heart failure that was refractory to diuretics and/or digitalis.

*Echocardiographic substudy:* An important issue in SAVE is whether there is a change in left ventricular size following infarction, and if this change can be modified by the use of captopril. In order to examine this issue, 773 patients randomized to SAVE agreed to participate in this substudy and had a baseline echocardiogram. On these studies, 5 views were obtained. Echocardiographic images were accepted only if there were at least 3 technically acceptable views, including ≥1 views examining the left ventricular short axis (mitral valve, high papillary muscle, and low papillary muscle levels) and the long axis (apical 4-chamber view and apical 2-chamber view). The data obtained in each of these analyses were reviewed for quality in the SAVE Echocardiogram Core Laboratory. On completion of this quality review, 512 of the 773 patients had baseline studies that were deemed technically acceptable. These patients receive repeat echocardiograms at 3 months, 1 year and 2 years postrandomization. These measures include left ventricular end-systolic and end-diastolic areas as well as contractile and noncontractile perimeters. Previous work has suggested that the extent of akinesis and dyskinesis at the baseline evaluation is an important covariate to correct for in the analysis of volume changes over time. Thus, it will be possible to present the results of the longitudinal echocardiographic analysis stratified by the extent of akinesis plus dyskinesis at baseline.

*Administrative organization:* The participating units of the trial—45 Clinical Centers, a Clinical Coordinating Center, a Data Coordinating Center, a RVG quality control laboratory, an electrocardiographic coding laboratory, and the Sponsor—are administratively linked via the study's principal investigator to encourage effective communication and to maintain the smooth operation of the trial. Each of the units was involved in the planning and development phase of the trial and contributed to the writing of the SAVE protocol and Manual of Operations.

A Steering Committee, composed of the SAVE Principal Investigators of each of the clinical centers, is the decision-making apparatus for the scientific and technical conduct of the study. The clinical centers have randomized the participants and are the units that dispense study medication. They record the regularly scheduled follow-up visits with the patients and complete the study forms that are forwarded to the Data Coordinating Center.

A Data and Safety Monitoring Committee is composed of scientists who are experts in clinical cardiology and biostatistics. This committee periodically reviews and evaluates study progress, including recruitment data, quality control, adverse effects of medication, and fatal and nonfatal events. The Data and Safety Monitoring Committee makes recommendations, as appropriate, regarding the safe conduct and continuation of the study. This Board has been guided in decisions involving the possible early termination of SAVE by statistical monitoring rules based on stochastic curtailment principles.[17,18]

The Clinical Coordinating Center is responsible for protocol modifications, financial disbursements, and monitoring clinical care decisions regarding adverse events. Each of the clinical units notifies the Clinical Coordinating Center when, based on the patient's clinical history and lack of response to nonvasodilator therapy for congestive heart failure, they believe their patient requires open-label captopril therapy. However, the Clinical Coordinating Center receives no information with respect to therapy group assignments. The Principal Investigator is involved in monitoring the trial's execution. He reports to the Data and Safety Monitoring Committee and the Steering Committees and receives only blinded interim analyses.

The Data Coordinating Center is responsible for performing the actual randomization of patients to SAVE. It receives all study forms, monitors the compliance of each of the clinical units with the protocol, and maintains the integrity of the data base. Unblinded information is presented by the Data Coordinating Center to the SAVE Data and Safety Monitoring Committee. In the rare event that a patient's clinical center is to be unblinded, the Data Coordinating Center, after investigation of the surrounding circumstances, informs the patient's physician of the therapy group assignment. Neither the Clinical Coordinating Center, study physician, nor the patient are given this information.

The Sponsor is informed of all logistical operations of the trial and attends the regularly scheduled Steering Committee meetings. The Sponsor has direct responsibility for the disbursement of study medication and study forms. The Sponsor receives information on the occurrence of serious adverse drug reactions but does not receive information about the identity of the patient's study medication unless there is a specific requirement by the government regulatory agencies, which is a rare event. The Sponsor does not attend the meetings of the Data and Safety Monitoring Committee. Therefore, the Sponsor has no knowledge of either therapy assignment or blinded results.

During the course of the trial the Clinical and Data Coordinating Centers jointly monitor the performance of the clinical centers and issues of protocol adherence are adjudicated by both coordinating centers in frequent telephone contacts. In addition, there are monthly conference calls between the Chairman of the Steering Committee, the Clinical Coordinating Center, the Data Coordinating Center, and the Sponsor during which operational and logistical issues of the trial are discussed. Reports are presented by the Data Coordinating Center and Clinical Coordinating Center to all center Principal Investigators and Sponsor during Steering Committee meetings held 3 times a year.

The Electrocardiogram Core laboratory is responsible for reviewing the baseline electrocardiograms of all SAVE participants and documenting this component of a myocardial infarction. This core unit also annually reviews required repeat electrocardiograms to detect clinically unreported recurrent nonfatal MI. Reports of nonfatal infarctions are confirmed by this core facility after correlating the clinical history, electrocardiogram, and enzyme criteria for recurrent MI.

The SAVE RVG Core laboratory overviewed the RVG of all patients selected by the Data Coordinating Center at baseline, permitting an assessment of RVG quality and confirming the presence of a low ejection fraction. It is also the responsibility of the RVG Core unit to review the final RVG of a subset of all participants after the RVG-EF has been evaluated by the clinical center.

The Ancillary Trials and Publications Committee reviews all applications for additional research involving SAVE study participants. Funding for the ancillary trials was established to foster research central to the clinical hypothesis of SAVE. Each of the SAVE investigators has the opportunity to participate in these ancillary studies. Approximately 15% of the total funds for SAVE, set aside for these additional research efforts, are allocated to projects approved by a committee of the investigators. In addition to the echocardiographic component, the major ancillary trials involve analyses of neurohormones, exercise tolerance, quality of life, ambulatory monitoring of electrocardiograms, and cardiac catheterization in the core laboratory.

An Endpoint Review Committee was assembled from the SAVE investigators in order to standardize the determination of end points in SAVE. This committee reviews the fatal end points that have occurred in the trial after documentation and verification of death has been assembled by the SAVE Data Coordinating Center. The committee codes the underlying cause of death as being one of the following:

- Atherosclerotic heart disease
  - Left ventricular dysfunction
  - Acute myocardial infarction
  - Unwitnessed death
  - Cardiac procedure
  - Heart transplant
  - Uncertain
  - Other
- Atherosclerotic vascular disease (excluding coronary artery disease)
- Nonatherosclerotic vascular disease
- Traumatic
- Cancer
- Other
- Unknown

The Endpoint Review Committee also attempts to identify the clinical status of the patient prior to death (e.g., reviewing New York Heart Association classification and Goldman classification), determining if the patient had experienced either ischemic or heart failure episodes after their randomization prior to their death. Results of these coding sessions are reported to the SAVE Data and Safety Monitoring Committee in its semiannual report.

## THE SAVE EXPERIENCE

**Screening:** Screening for SAVE commenced in January 1987 and was completed in January 1990. This process revolved around the continued surveillance of SAVE clinical center intensive care and coronary care units, an examination undertaken by 45 clinical centers and their 112 satellite facilities in the United States and Canada. Only patients in the early (3–16 days postinfarction) convalescent period of MI were considered. A SAVE MI was considered to have occurred if the patient experienced either (1) acute changes in an electrocardiogram (Q or QS finding plus ST elevation and/or T-wave inversion plus absence of left bundle branch block or Wolff-Parkinson-White syndrome) obtained shortly after the infarction with the attendant clinical symptoms and elevation in myocardial enzymes or (2) the presence of changes in Q waves on serial electrocardiograms demonstrated an MI had occurred or (3) the patient had an elevation of myocardial enzymes that were twice as high as normal levels and typical symptoms of a MI were present. The patients were then evaluated for SAVE inclusion and exclusion criteria (Table I). The patients who were not excluded then had their RVG-EF measured. Objective evidence of left ventricular dysfunction was defined as a resting RVG demonstrating a RVG-EF of $\leq 40\%$.

The SAVE screening experience is summarized in Table II. Between 1987 and 1990, 95,856 coronary care unit patients were screened, of which

36,630 (38.2%) sustained an MI based on the attending physician's judgment. Of these, 31,010 survived the initial 72 hours in the hospital and were age eligible. Of these 31,010 patients, 18,935 (61.1%) had ejection fractions >40% (as determined by either clinical assessment, nuclear, echocardiographic, or contrast ventriculography), and 575 patients (1.9%) did not meet the SAVE criteria for MI and were excluded. There were 2,562 patients (8.3%) who could not be randomized during the 16-day window. The exclusion reasons for 4,873 patients of the remaining 8,938 are provided in Table II. There were 4,065 patients who had a SAVE-eligible MI, did not have any specific exclusion criteria, and had a nuclear ejection fraction of ≤40%. Of these, 1,178 were already on an ACE inhibitor although this was not required for management of clinical congestive heart failure. In 367 patients, ischemia was either manifested clinically or by exercise testing and an evaluation was not pursued within the 16-day window for randomization. There were 270 patients who did not consent to participate in the trial. All consenting patients were required to receive a test dose of open-label captopril (6.25 mg). Nineteen patients were excluded because of either orthostatic or ischemic symptoms attributed to administration of study medication. This left 2,231 patients for randomization into the trial.

**TABLE II** Screening Experience of SAVE

| | | |
|---|---|---|
| January 27, 1987–January 31, 1990 | | |
| 95,856 | Coronary care unit admissions screened | |
| | → 59,226 | no clinical MI |
| 36,630 | Clinical MI | |
| | → 5,620 | death or age ineligible |
| 31,010 | Clinical MI<br>Survived initial 72 hours<br>Age eligible (21–79) | |
| | → 18,935 | EF assessed as >40% |
| | → 575 | no SAVE MI |
| | → 2,562 | >16 days after MI |
| 8,938 | SAVE Exclusions (4,873) | |
| | → 25 | women of childbearing potential |
| | → 64 | previous hypersensitivity to captopril |
| | → 10 | neutropenia |
| | → 35 | systemic lupus erythematosus or scleroderma |
| | → 702 | serum creatinine >2.5 mg/dl |
| | → 635 | congestive heart failure requiring vasodilation |
| | → 104 | hypertension requiring vasodilator therapy |
| | → 911 | other illness precludes patient involvement |
| | → 294 | unstable postmyocardial function course |
| | → 1,750 | patient unwilling or unable to participate (psychologic disorder, history of poor compliance, geographic distance precludes involvement, patient' involved in other clinical trials) |
| | → 125 | excluded for other reason |
| | → 218 | death during screening |
| 4,065 | No exclusions | |
| | → 1,178 | already on ACE inhibition |
| | → 367 | ischemia not evaluated within 16 days |
| | → 270 | nonconsenting |
| | → 19 | orthostasis or ischemia after test dose |
| 2,231 | Randomized to SAVE | |

ACE = angiotensin-converting enzyme; EF = ejection fraction; M = myocardial infarction; SAVE = Survival and Ventricular Enlargement.

The randomization procedure began with a telephone call to the SAVE Data Coordinating Center. During the ensuing conversation, the clinical center relayed the demographic and clinical characteristics of the patient being randomized. The patient's age, elapsed time since the MI, RVG-EF, potential exclusion criteria, and the patient's tolerance to the test dose were reviewed. In addition, the clinical center provided assurance that the patient is not in clinical congestive heart failure at the time of randomization. After the Data Coordinating Center agreed that the patient had satisfied all entry criteria for SAVE, the patient was assigned a randomization number based on a random number generator implementing a variable block-size feature. The randomization number was then used by the clinical centers, core laboratories, and coordinating centers in identifying this patient.

**Baseline findings:** A summary of the baseline findings of randomized participants is included in Table III. The average age of the randomized cohort was 59.4 years. More than 82% of the cohort were male, and 89.3% were white. The mean baseline RVG-EF was 31.0%, and, on average, 11 days elapsed between the SAVE MI and randomization. Between the index MI and randomization, 32.7% received thrombolytic therapy, 55.2% of the cohort had cardiac catheterization, 17% underwent percutaneous coronary angioplasty, and 9.1% had coronary artery bypass surgery.

**Follow-up procedures:** Follow-up visits serve both to secure consistent health care delivery, accomplish surveillance of trial end points, and to both enhance and monitor compliance to study medication. Patients were evaluated at 2 weeks and 3 months postrandomization, and then every 3 months during the first year of follow-up. Thereafter, visits are scheduled at 4-month intervals until the completion of the study. The evaluation at these visits includes a history and physical examination, assessment of functional capacity, determination of the occurrence of heart failure or cardiovascular complications, and the occurrence of adverse

**TABLE III** Baseline Characteristics of the SAVE Cohort

| Characteristic | Population (n = 2,231) |
|---|---|
| Mean age (yrs) | 59.4 (SD = 10.6) |
| Gender (%) | |
| Male | 82.5 |
| Female | 17.5 |
| Race (%) | |
| White | 89.3 |
| Black | 5.6 |
| Other | 5.0 |
| SAVE MI criteria (%) | |
| Symptoms, ECG, and enzymes | 78.4 |
| ECG alone | 2.1 |
| Symptoms and enzymes | 19.5 |
| Mean LV ejection fraction | 31.0 (SD = 6.7) |
| Mean number of days between MI and randomization | 10.9 (SD = 3.3) |
| Highest educational level (%) | |
| Less than high school | 36.7 |
| High school graduate, not college graduate | 46.2 |
| College graduate | 10.9 |
| Postgraduate | 6.2 |
| History of diabetes (%) | 22.0 |
| Family history of heart disease (%) | 46.0 |
| History of hypertension (%) | 43.0 |
| History of chronic CHF (%) | 5.8 |
| Significant valvular disease | 4.1 |
| Other cardiac disease | 8.7 |
| Procedures between SAVE MI and randomization | |
| Cardiac catheterization (%) | 55.2 |
| PTCA (%) | 17.0 |
| Coronary thrombolysis (%) | 32.7 |
| CABG | 9.1 |

CABG = coronary artery bypass graft; CHF = congestive heart failure; ECG = electrocardiogram; LV = left ventricular; MI = myocardial infarction; PTCA percutaneous transluminal coronary angioplasty; SAVE = Survival and Ventricular Enlargement.

drug reactions. In addition, counseling for reduction of cardiac risk factors occurs at each visit. At each evaluation, intervening illnesses, surgical operations, and alterations in the medical regimen are noted. On all visits titration of the study drug is considered until the target dose of 150 mg daily is achieved. Patients are instructed to return all unused medications, and pill counts are used to assess patient compliance. Postrandomization laboratory evaluations include a complete blood count, blood urea nitrogen, creatinine, and serum potassium at the 2-week visit and at yearly intervals.

A repeat determination of left ventricular ejection fraction using the same RVG-EF technique utilized during the SAVE screening process is performed at the termination of the study. This terminal RVG-EF is being obtained after the patient's study medication has been discontinued for 48 hours. In patients who develop symptomatic heart failure requiring ACE inhibitor therapy prior to the study's completion, an additional RVG-EF was requested prior to administration of open-label therapy. In order to ensure a high quality RVG, a significant fraction of the acute RVG-EF's were overread. In circumstances of multiple RVG-EFs obtained during the course of the follow-up period, only the last RVG-EF will be used in the assessment of the primary end point of SAVE. The timing of the last RVG-EF depends on the length of time patients have been in the study. Patients who were randomized in 1987 are to have their terminal RVG-EFs measured starting April 1991, whereas patients randomized in 1988 and 1989 are scheduled for their terminal RVG-EF commencing in the summer and fall of 1991, respectively.

*Adherence:* It was recognized from the initial planning phase of SAVE that maintaining the success of this major endeavor would be heavily dependent on the ability of the clinical centers to carry out the SAVE protocol successfully. To that end, the Clinical and Data Coordinating Centers have worked jointly to develop measuring devices to monitor the abilities of the clinical centers to maintain the randomized participants on study medications. These procedures begin with the creation and dissemination to the clinical centers from the Data Coordinating Center of a list of patients who fall in each of the following categories: (1) off study medication; (2) patients who are on study medication but not at target dose; (3) patients with delinquent follow-up forms; and (4) patients who have died but whose documentation is incomplete.

Each month, the Clinical Coordinating Center and Data Coordinating Center jointly review the progress of the clinical centers in minimizing the number of randomized participants off study medication, those participants on study medication but not at target dose, and those patients whose follow-up forms are delinquent. After this review, letters are sent from the Data Coordinating Center to those centers at which a special effort is believed to be required to improve performance with regard to these measures.

**Statistical methodology:** A number of different statistical procedures have been utilized to examine the many different issues raised by the SAVE study. Chi-square statistics and 2-sample *t*-tests have been used to evaluate differences in baseline characteristics between the placebo and treatment groups.

To evaluate the importance of differences between the curves for mortality and each of the specified clinical end points of the two groups, Cox proportional hazard models will be used. This procedure allows the time until death to be considered in evaluating the difference between survival curves. In addition, this method permits the evaluation of the effect of treatment after taking into account the influences of baseline characteristics such as age, ejection fraction, gender, history of prior myocardial infarction, and cardiac procedures prior to randomization.

*Proposed analysis of the primary end point:* The primary end point of SAVE is the occurrence of either death or survival and a $\geq 9$ unit reduction in ejection fraction as determined by RVG-EF. The analysis of this event will consider the time to the patient's death or the time until a change in RVG-EF $\geq 9$ for patients who survive. Every patient randomized to the study has a radionuclide ventriculogram during their initial examination for trial suitability (baseline RVG-EF). If a patient dies during the follow-up period of the trial, that participant's primary end point is considered to have occurred, and his time to death examined. In addition, all survivors will have an RVG-EF performed at the study's end (terminal RVG-EF). If this terminal RVG-EF has deteriorated by $\geq 9$ units (baseline RVG-EF minus the terminal RVG-EF is $\geq 9$, i.e., $\Delta$RVG-EF $\geqslant 9$), an end point has occurred. A statistical analysis based on that of Gehan[19] will simultaneously consider both mortality information and data from the RVG-EF component of the combined end point, providing for maximum power to test the clinical hypothesis of SAVE.

## SUMMARY

An important cause of death in the post-MI population is congestive heart failure, a major sequela of the infarction process. Whether pharmacologic treatment with an ACE inhibitor will reduce the occurrence of postinfarction congestive heart failure and therefore improve survival is unknown. The results of SAVE are expected to be available in 1992, providing an average follow-up period of 3.5 years, and 7,742 patient-years of postinfarction survival information. This repository of patient experience may help in the identification of a pharmacologic regimen that will result in improved survival following MI.

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## APPENDIX

**Principal Investigator:** Marc A. Pfeffer, MD, PhD.

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# Activation of Neurohumoral Systems Following Acute Myocardial Infarction

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**Previous studies have indicated that patients with an acute myocardial infarction have marked activation of all neurohumoral systems on admission to the hospital. This activation begins to subside within the first 72 hours so that by 7–10 days, all plasma neurohormones have returned to normal. The only documented exceptions were found to occur in patients with left ventricular dysfunction and overt heart failure, where both plasma renin activity and atrial natriuretic peptide were increased, and in patients with left ventricular dysfunction but no overt heart failure, where only atrial natriuretic peptide was increased. Although these studies suggest that neurohumoral activation rarely occurs at the time of hospital discharge, they were small and may have missed an important subgroup of patients with persistent neurohumoral activation. In the Survival and Ventricular Enlargement (SAVE) study, 522 patients had plasma neurohumoral levels measured at a mean of 12 days postinfarction. All SAVE patients had left ventricular dysfunction (left ventricular ejection fraction ≤40%), but no overt heart failure. In this group of patients, all neurohumoral levels (plasma renin activity, norepinephrine, arginine vasopressin, and atrial natriuretic peptide) were found to be increased compared with age-matched control subjects. These results indicate that, in fact, a subgroup of patients without overt heart failure has persistent neurohumoral activation at the time of hospital discharge postinfarction, and that this activation involves several neurohumoral systems. Since patients with persistent neurohumoral activation postinfarction are likely those most at risk of developing complications and the ones most likely to benefit from pharmacologic interventions blunting the effects of neurohumoral activation, measurement of predischarge neurohumoral levels may be useful.**

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Patients with acute myocardial infarction have been shown to have marked neurohumoral activation.[1–27] During the first 72 hours postinfarction, virtually all measured neurohumoral levels are increased, and in some cases to very high levels (Figures 1, 2, 3 and 4). Although all neurohumoral systems are activated, the extent and pattern with which each system is activated varies widely. Later, neurohumoral activation subsides so that by 7–10 days, circulating neurohumoral levels have returned to normal in the majority of patients.[1,3,4,8,9,12,22,23,27] The only exceptions are patients with overt heart failure in whom chronic activation of the renin–angiotensin system and atrial natriuretric peptide have been shown to occur, and patients with left ventricular dysfunction without overt heart failure, in whom atrial natriuretic peptide is increased.[1,3,8,22,23,27] Patients with cardiogenic shock have activation of all neurohumoral systems, including the sympathetic nervous system.[4,9]

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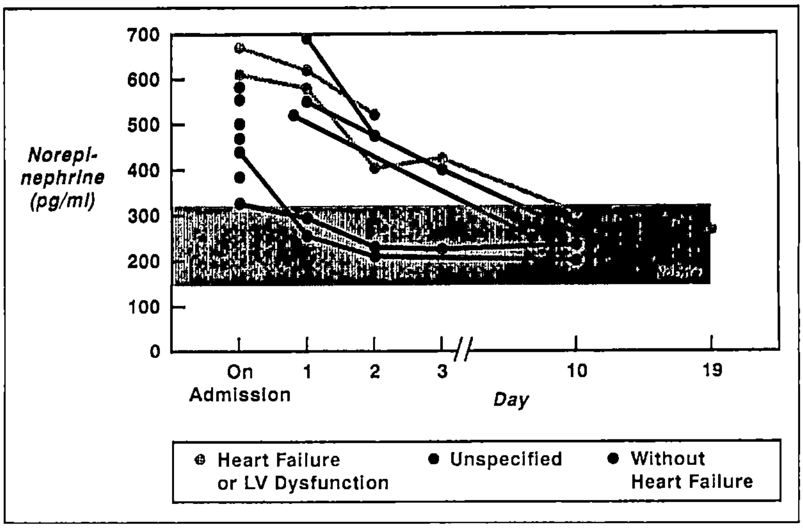

**FIGURE 1. Summary of studies evaluating plasma norepinephrine levels postinfarction. Normal values (mean ± standard deviation of age-matched controls) are indicated by shaded area. LV = left ventricular.**

## ACTIVATION OF SPECIFIC NEUROHUMORAL SYSTEMS

Activation of the sympathetic nervous system occurs nearly immediately postinfarction.[1–13] The extent to which it is activated has been related to infarct size and to the degree of left ventricular dysfunction.[1,2,4–6,9,13] Nevertheless, increased circulating catecholamines have also been documented in patients with smaller myocardial infarctions and no evidence of left ventricular dysfunction.[1,3,5,9] Not surprisingly, patients with higher circulating catecholamines have been found to have a poorer prognosis.[2,4,5,9,11,13] What proportion of this is the result of increased catecholamines and what proportion is the result of left ventricular dysfunction remains to be determined. Certainly, studies documenting improved survival with the use of intravenous β blockers in acute myocardial infarction argue in favor of at least a partial direct deleterious effect of the catecholamines themselves.[28,29] Also, since intravenous β blockers are generally well tolerated, it would appear that this early increase in catecholamines is not frequently necessary to maintain adequate ventricular function.

Gradually, over the following 10 days, activation of the sympathetic nervous system has been shown to subside even in patients with left ventricular dysfunction.[1,3,8,27] These results appear to be inconsistent with studies showing improved survival when β blockers are started prior to hospital discharge. At least three possibilities exist to explain this apparent discrepancy. First, because the

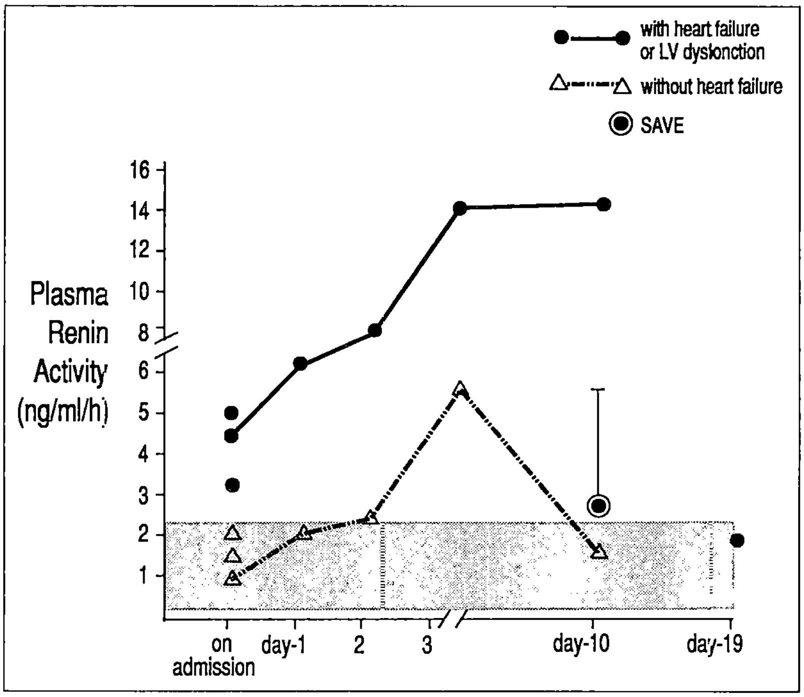

**FIGURE 2. Summary of studies evaluating plasma renin activity postinfarction. Normal values (mean ± standard deviation of age-matched controls) are indicated by shaded area. LV = left ventricular.**

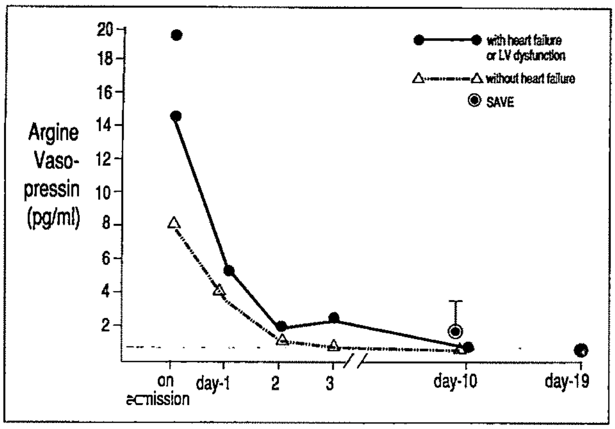

**FIGURE 3. Summary of studies evaluating arginine vasopressin levels postinfarction. Normal values (mean ± standard deviation of age-matched controls) are indicated by shaded area. LV = left ventricular.**

number of patients with left ventricular dysfunction in these studies was small, a subgroup of patients with a persistent increase in sympathetic tone may have been missed. Such a subgroup of patients would be expected to benefit most from β blockers. It is also possible that measuring circulating catecholamines at rest is an inappropriate way of assessing adrenergic function. Circulating norepinephrine is known to represent only a fraction of the norepinephrine released by nerve terminals[30,31] and resting norepinephrine values may miss significant increases during exercise. Or, alternatively, it may be that postinfarction patients are particularly sensitive to an increase in adrenergic tone and that any blunting of the catecholaminergic stimulation is beneficial to the patients.

Activation of the renin–angiotensin system occurs early postinfarction in nearly all patients; however, its peak activation occurs somewhat later than that of catecholamines[1–3,14,15] (Figure 2). Initially, activation appears to occur only in patients with left ventricular dysfunction.[1,15] However, by 72 hours, nearly all patients have an increase in plasma renin activity, regardless of infarct size or ventricular function.[1] The reason for this delay in peak activation is uncertain but may be related to suppression of renin release by high circulating vasopressin levels.[32,33] Plasma renin activity is thought to increase as a result of a combination of acute reduction of renal blood flow, increased renal nerve activity, increased sympathetic tone and, in the case of patients with heart failure, to the contraction of blood volume associated with the use of diuretics.[34,35] Increased plasma renin activity has also been found to be associated with increased postinfarction mortality.[2,15] Whether this association is the result of the direct effects of increased plasma renin activity itself, to its association with worse left ventricular function, or to the effects of simultaneously activated neurohumoral systems remains to be determined.

As opposed to circulating catecholamines, when diuretics are used, plasma renin activity remains elevated until after hospital discharge.[1,27] When diuretics are not used, plasma renin activity gradually returns to normal so that even patients with asymptomatic left ventricular dysfunction have normal plasma renin activity at hospital discharge.[1,27] Nevertheless, when patients with left ventricular dysfunction not taking diuretics are further subclassified according to Killip class or more severe left ventricular dysfunction, there appears to be a difference in activation of the renin–angiotensin system.[27] Although both groups have plasma renin activities in the normal range, patients with a higher Killip class or worse ventricular function have higher plasma renin activities than patients with a lower Killip class or better ventricular function. Whether a subgroup of patients not

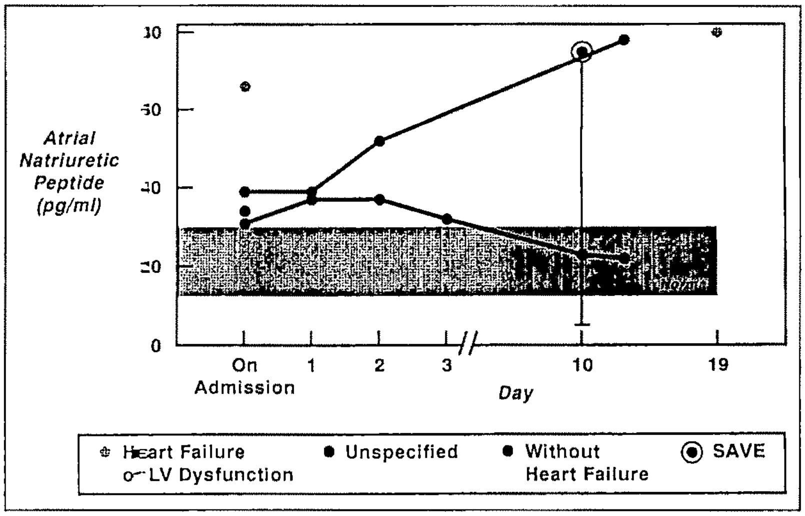

**FIGURE 4. Summary of studies evaluating atrial natriuretic peptide levels postinfarction. Normal values (mean ± standard deviation of age-matched controls) are indicated by shaded area. LV = left ventricular.**

receiving diuretics actually has a long-term increase in plasma renin activity remains to be determined. However, results of animal[36] and clinical[37,38] studies indicating that angiotensin-converting enzyme (ACE) inhibitors maintain ventricular function and prevent ventricular dilation postinfarction are compatible with some kind of long-term activation of the renin–angiotensin system postinfarction.

Plasma arginine vasopressin increases rapidly in all patients with acute myocardial infarction,[1,2,24] an increase that is thought to be at least partly the result of the use of narcotic analgesics[39,40] (Figure 3). By 72 hours, circulating arginine vasopressin has generally been found to have returned to normal.[1] Patients with heart failure are the exception, arginine vasopressin values remaining elevated in these patients until 7–10 days postinfarction.[1] Why arginine vasopressin increases during the hyperacute postinfarction period is not known, but it may be related to the degree of activation of other neurohumoral systems, to hemodynamic and cardiac changes, and/or to the stress associated with the acute myocardial infarction.[41–44] Increased arginine vasopressin levels have been correlated with a poorer survival,[2,24] an effect that may be related to its deleterious myocardial or coronary vascular effects when present in high concentrations.[45–48] High levels of arginine vasopressin have been shown to cause coronary vascular spasm, myocardial infarction, arrhythmias, and sudden death.[45–48] Alternatively, the association between arginine vasopressin and survival may simply be the result of poorer left ventricular function or of the effects of other simultaneously activated neurohumoral systems. In addition to being associated with a poorer survival, the antidiuretic effect of arginine vasopressin may also contribute to the hyponatremia,[25,49] fluid overload,[49] and pulmonary congestion of postinfarction patients.

Atrial natriuretic peptide also increases acutely postinfarction[16–23,27] (Figure 4). However, as opposed to other measured neurohormones, it remains elevated in all patients with left ventricular dysfunction[22,23,27] and this for at least 3 weeks postinfarction.[27] Increased atrial natriuretic peptide is presumably the result of increased ventricular filling pressures and appears to be less marked when thrombolysis has been used.[18,19] Increased atrial natriuretic peptide synthesis postinfarction occurs not only in the atria, but also in the ventricle,[20,21] the increase in ventricular synthesis being largest in patients with extensive myocardial infarctions.

## THE SAVE EXPERIENCE

The Survival and Ventricular Enlargement (SAVE) study is a randomized multicenter trial designed to evaluate the effects of the ACE inhibitor captopril on improving survival and reducing cardiovascular mortality and the incidence of a major deterioration in ejection fraction in survivors of acute myocardial infarction with baseline left ventricular dysfunction. Randomization into the SAVE study occurred between 3 and 16 days after the acute onset of myocardial infarction. In addition to having the acute infarction, patients had to be $>21$ and $<80$ years of age and have a radionuclide left ventricular ejection fraction of $\leq 40\%$ to be eligible for inclusion in SAVE. Contraindications to captopril and concurrent medical problems such as renal insufficiency (serum creatinine $>2.5$ mg/dl), severe valvular disease, refractory hypertension, malignancy, or other conditions thought to limit survival were study exclusions. Patients clinically manifesting congestive heart failure despite treatment with digitalis and/or diuretics were also ineligible, as were patients with ischemic symptoms or with a markedly positive exercise test, unless cardiac catheterization and appropriate revascularization procedures were conducted prior to randomization. Eligible patients were required to provide written, informed consent.

The average age of these 522 patients was 60 ± 11 years; 428 patients were male and 94 were female. Their mean arterial pressure was 84 ± 11 mm Hg, their mean heart rate was 77 ± 29 beats/min, and their mean ejection fraction was 31%. One third of the patients took diuretics, one third took digoxin, one third took β blockers, and one quarter took calcium antagonists. A group of 38 normal, age-matched persons with no obvious illnesses or cardiac disease and taking no medications were used as control subjects.

Prior to randomization, after an overnight fast, and once the patient had been lying in a supine position for at least 30 minutes, circulating neurohormones (norepinephrine, plasma renin activity, atrial natriuretic peptide, and arginine vasopressin) were obtained through an indwelling catheter already in place for $>30$ minutes. This occurred a mean of 12 days postinfarction. Plasma neurohormones were measured according to methods previously described.[50,51]

In this large group of patients with left ventricular dysfunction but no overt heart failure, a large number of patients were found to have an increase in circulating neurohumoral levels around the time of hospital discharge. Plasma norepinephrine (Figure 1), plasma renin activity (Figure 2), plasma arginine vasopressin (Figure 3), and atrial natriuretic peptide (Figure 4) were all found to be increased.

## POTENTIAL SIGNIFICANCE OF SAVE RESULTS

Persistent neurohumoral activation postinfarction would help explain the beneficial effects of β blockers[28,29] and ACE inhibitors[36–38] postinfarction. Beta blockers have been found to be particularly useful in improving survival in patients with left ventricular dysfunction postinfarction, even when they are started around the time of hospital discharge.[52] ACE inhibitors, for their part, have been found to be useful in preserving left ventricular function and geometry after large myocardial infarction.[37,38] Their effects on survival are presently under investigation in the SAVE study. Nevertheless, despite the generally beneficial effects of pharmacologic interventions that block the effects of neurohumoral activation, it remains to be determined whether patients with neurohumoral activation are those at highest risk of long-term complications or even whether neurohumoral activation persists after hospital discharge.

How neurohumoral activation in these patients compares with that of patients with chronic asymptomatic or symptomatic heart failure is illustrated in Figure 5. When compared to the Studies of Left Ventricular Dysfunction (SOLVD)[53] asymptomatic (prevention) group, SAVE patients had similar plasma norepinephrine values but higher plasma renin activity, arginine vasopressin, and atrial natriuretic peptide. Compared with the SOLVD symptomatic (treatment) group, SAVE patients had lower plasma norepinephrine and renin activity, similar atrial natriuretic peptide, and greater arginine vasopressin levels. Thus, neurohumoral activation in the SAVE patients was somewhere between that of the SOLVD asymptomatic and symptomatic heart failure groups.

In patients with chronic heart failure, neurohumoral activation has been associated with a poorer prognosis.[54–57] Although never proven, there are a number of theoretical reasons to believe that chronic neurohumoral activation may also be deleterious in postinfarction patients. Chronic activation of the sympathetic nervous system can predispose to serious ventricular arrhythmias.[58,59] Postinfarction, a decrease in heart rate variability, a reflection of increased sympathetic and decreased parasympathetic tone, is associated with a poorer prognosis,[60,61] and the use of β blockers decreases the incidence of sudden death in postinfarction patients.[52] Activation of the sympathetic nervous system, the renin–angiotensin system, and

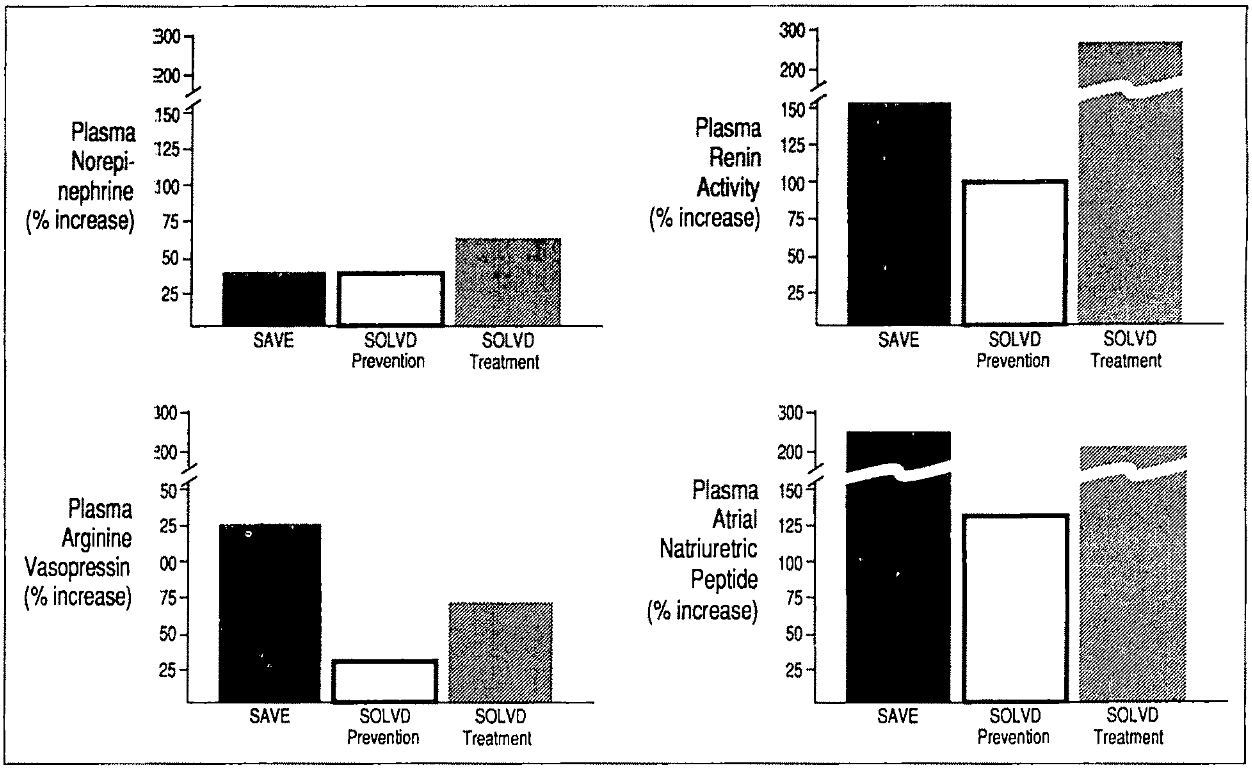

**FIGURE 5. Comparison between the increase in neurohumoral levels of the SAVE patients and the SOLVD prevention (asymptomatic) and treatment (symptomatic) groups. SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction.**

increased arginine vasopressin levels can contribute to the development of worsening heart failure, and thus to a poorer prognosis,[62] by increasing afterload and preload.[63,64] Neurohumoral activation can also lead to ventricular dilation and thus to a poorer prognosis.[65] Neurohumoral activation causes ventricular dilation by increasing preload and afterload, which can, of itself, contribute to the development of ventricular dilation.[66–70] Neurohumoral activation may also lead to ventricular dilation by directly stimulating protein synthesis.[71–73]

Thus, activation of all neurohumoral systems occurs during the hyperacute phase of a myocardial infarction. By hospital discharge, circulating neurohumoral levels have generally returned to normal. Nevertheless, in a subgroup of patients with left ventricular dysfunction but no overt heart failure, neurohumoral activation persists. What neurohumoral activation at this time means for the patient or even whether neurohumoral activation persists for any further period of time remains to be determined. However, there is reason to believe that neurohumoral activation at hospital discharge may identify patients with a worse prognosis and may be useful in identifying patients at most need of close follow-up and therapeutic interventions. These hypotheses are being tested by the follow-up portion of the SAVE study.

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# Fourth International Study of Infarct Survival: Protocol for a Large Simple Study of the Effects of Oral Mononitrate, of Oral Captopril, and of Intravenous Magnesium

ISIS-4 Collaborative Group

The fundamental aim of the International Studies of Infarct Survival (ISIS) collaborative group is to assess reliably the balance of any benefits and risks for widely practicable treatments that might produce moderate but worthwhile mortality reductions in patients with suspected acute myocardial infarction. Substantial numbers of lives might be saved by such treatments, but benefits of the size that can realistically be expected may be reliably detected only by randomized trials involving some tens of thousands of patients. In order to recruit such numbers, ISIS involves almost no extra work for collaborators: hence, busy general hospitals—where the majority of acute myocardial infarction patients are actually treated—can take part easily. The ability of the ISIS trials to yield clear, reliable answers depends entirely on the collaboration of many doctors and nurses in the participating hospitals. For this reason, publication of the final results is in the names of all the collaborators.

All patients, high risk as well as low risk, presenting within 24 hours of the onset of suspected acute myocardial infarction are eligible for ISIS-4, provided that the responsible physician does not initially consider there to be any clear indications for, or clear contraindications to, any one of the trial treatments—nitrate, angiotensin-converting enzyme inhibitor, or magnesium. Patients are randomized between 1 month of oral controlled-release mononitrate or placebo; between 1 month of oral captopril or placebo; and between 24 hours of intravenous magnesium or open control (i.e., no infusion). (Patients who are to be given intravenous or other non-trial nitrate for just a few days can still be entered.) In this trial, 3 quite different treatments will each be evaluated. At first glance, this may appear to complicate the results, but in fact appropriate statistical analysis of this "factorial" design will allow all patients to contribute fully to assessment of the separate effects of each treatment (while also providing important information about the combined effects). Apart from giving the trial treatments, all other aspects of individual patient management are left entirely to the responsible physician to decide. For example, previous trials in suspected acute myocardial infarction have shown that, for many categories of patients, antiplatelet and fibrinolytic therapy can save lives. Hence, most collaborating doctors will wish to give antiplatelet therapy routinely and to start fibrinolytic therapy in many of their patients before randomizing them in ISIS-4. Some physicians may also wish to use certain other treatments (such as intravenous β blockers, anticoagulants) routinely in particular categories of patients. There are no restrictions on this in ISIS-4. Thus, ISIS-4 will provide good evidence about the effects of adding the trial treatments to various standard treatments. By including many different types of patients from many different types of hospitals with a wide variation in ancillary management (which is in any case unavoidable), the ISIS-4 results will be of direct clinical relevance to the heterogeneous realities of clinical practice worldwide.

(Am J Cardiol 1991;68:87D–100D)

The chief aim of the Fourth International Study of Infarct Survival (ISIS-4) is the reliable assessment of the separate and combined effects on vascular mortality of adding 3 widely practicable treatments—1 month of oral controlled-release mononitrate (Indur), 1 month

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of oral captopril (Capoten), and 24 hours of intravenous magnesium—to currently standard treatments for a wide range of types of patients (high risk as well as low risk) with definite or suspected acute myocardial infarction (MI).

## CHOICE OF TREATMENTS TO STUDY

**A practicable nitrate regimen: once-daily oral controlled-release mononitrate for one month:** Nitrates may reduce myocardial workload during acute MI by reducing peripheral resistance and blood pressure, and may increase myocardial perfusion.[1,2] They have been shown, not only in experimental animals but also in clinical studies, to limit infarct size and to improve left ventricular function and remodeling.[1]

Only about 3,000 acute MI patients have thus far been studied in randomized trials of nitrates, generally of short duration (i.e., just a few days). Individually, the mortality results from these trials are somewhat inconclusive, but an overview of them is promising, suggesting that mortality may have been reduced by about one third[3] (Table I). Oral nitrates have been less widely studied than intravenous nitrates. Tablets are, however, simpler to give than intravenous infusions, particularly if treatment is to be maintained beyond the first day or two. So, if 1 month of oral nitrate can be shown reliably by ISIS-4 to save lives, this might be used extensively in future practice.

**TABLE I** Reductions in Mortality in an Overview of the Results of Previous Randomized Trials of Short-Term Nitrates in Acute Myocardial Infarction

| Regimen (generally of short duration) | Apparent Reduction (% ± SD) in Mortality |
|---|---|
| Intravenous nitrates | 35% ± 10 |
| Oral nitrates | 21% ± 17 |
| Any nitrate | 31% ± 9 |

Especially when indicated for the relief of symptoms, intravenous or other short-term nitrate use is already quite widespread, and longer-term use of nitrates is now being considered. Continuous exposure to nitrates can, however, lead to a state of pharmacologic tolerance that limits their clinical efficacy. In the present study, therefore, a once-daily regimen of a controlled-release formulation (Durules) of isosorbide-5-mononitrate (Imdur) has been adopted that minimizes the development of tolerance,[4] perhaps because the plasma nitrate levels are low for a period overnight. Tolerance to nitrates may, in part, involve reflex activation of the renin–angiotensin system,[5] in which case the combination of a nitrate and an angiotensin-converting enzyme (ACE) inhibitor in ISIS-4 may be particularly effective.

**A practicable angiotensin-converting enzyme inhibitor regimen: twice-daily oral captopril for one month:** The renin–angiotensin system is activated in acute MI,[6] leading to stimulation of the heart and to increased systemic and coronary vascular resistance. As a result, myocardial oxygen requirements may be increased and supply decreased, which may lead to infarct extension. Increases in systemic vascular resistance may also increase myocardial wall stress, predisposing to aneurysm or to progressive ventricular dilation during the recovery phase following infarction. ACE inhibitors, such as captopril, might prevent some of these adverse effects.[7] In animals, studies of ACE inhibitors in the acute phase of infarction provide some evidence that infarct size can be reduced, while continued use of an ACE inhibitor following experimental infarction has been shown to improve ejection fraction, ventricular remodeling and, possibly, survival.[8]

In patients, long-term use of ACE inhibitors has been shown to improve cardiac function substantially in chronic congestive cardiac failure[9] and in the later recovery phase following myocardial infarction.[10,11] Experience with ACE inhibitors in acute MI is more limited, but for several hundred patients in the pilot studies for ISIS-4[12–14] and in other controlled studies,[15] oral captopril was well tolerated (even by high-risk patients, and by those receiving fibrinolytic therapy, nitrates, and magnesium). Improvements in cardiac function were seen within 1 hour of starting treatment in the acute phase of infarction, and these benefits persisted after the end of treatment (Figure 1). ISIS-4 is designed to provide reliable information as to whether the use of an ACE inhibitor during, and in the month just after, a suspected acute MI also improves survival.

**A practicable magnesium regimen: 24-hour intravenous infusion of magnesium sulfate:** Increasing serum magnesium levels in experimental infarction can prevent myocardial damage, perhaps by inhibiting calcium influx into ischemic myocardial cells and by reducing coronary artery tone. Infusions of magnesium in animal studies have also been shown to increase the threshold for electrical excitation of myocardial cells, thereby reducing the likelihood that injury currents near ischemic or infarcted tissue lead to cardiac arrhythmias.[16] Elevation of serum magnesium in humans reduces peripheral vascular resistance and increases cardiac output without any corresponding increase in cardiac work. Thus, magnesium infusions started early after the onset of myocardial ischemia may limit infarct size, prevent serious arrhythmias, and reduce mortality.

Contraindications, if any, to magnesium infusions are few, and treatment regimens that can produce an approximate doubling in serum magnesium levels are simple to administer (i.e., an initial short "bolus" infusion followed by a longer "maintenance" infusion) and apparently safe. The only common adverse effects are a feeling of warmth and some tingling and flushing of the skin, particularly if the initial bolus infusion is given too rapidly (i.e., over less than 10–15 minutes). Collectively, the first few randomized trials of magnesium infusion in acute MI indicate quite a large mortality reduction (Table II).[17] However, the total number of patients studied in those trials is small, so this result cannot be considered really reliable. ISIS-4 provides a unique opportunity to assess accurately any real effects of magnesium on the risk of death in a wide range of patients with suspected acute MI.

**Flexibility in the use of antiplatelet and fibrinolytic therapy, and in all other aspects of management (including intravenous or other nontrial nitrate for just a few days):** Antiplatelet therapy (such as aspirin) in acute MI significantly reduces death, stroke, and reinfarction and has few side effects.[18] It is recommended, therefore, that (unless a strong contraindication is believed to exist) antiplatelet therapy should begin immediately, which will generally be before randomization into ISIS-4. Likewise, because fibrinolytic therapy significantly reduces mortality in many types of patient with acute MI,[18] it is also recommended that (wherever it is thought to be indicated) any fibrinolytic therapy should generally be started before randomization. Patients are, of course, eligible for entry into the trial, irrespective of whether or not antiplatelet or fibrinolytic therapy is used.

**TABLE II** Reduction in Mortality in an Overview of Seven Small Randomized Trials of Intravenous Magnesium in Acute Myocardial Infarction

| Allocated Magnesium | Allocated Control |
|---|---|
| 25/657 (4%) | 53/644 (8%) |

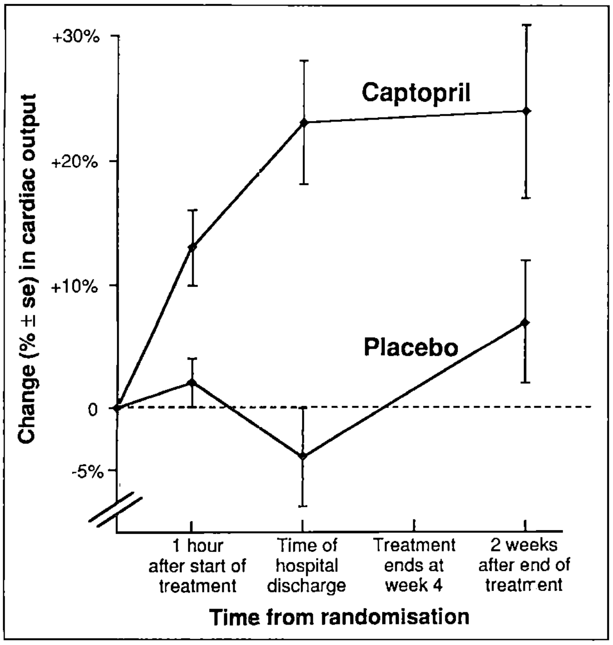


**FIGURE 1. Increase in cardiac output with captopril in the ISIS-4 pilot study. se = standard error.**

In general, physicians who definitely want to use one or other of the trial drugs (i.e., nitrate, ACE inhibitor, or magnesium) in a particular patient should do so, and should not randomize that patient. There is one exception to this general rule: even though the testing of 1 month of oral controlled-release mononitrate forms part of ISIS-4, patients can still be randomized if intravenous or some other non-trial nitrate is to be used for just a few days. Otherwise, after randomization, non-trial nitrate, non-trial ACE inhibitor, or non-trial magnesium should be used only if a clear indication is thought to have developed.

All other aspects of patient management (such as the use of intravenous β blocker, anticoagulant) are entirely at the discretion of the responsible physician, for the needs of individual patients and the preferred methods of different physicians vary widely. The wide variation in the ancillary management of trial patients that will result (and which is anyway unavoidable) is advantageous, since it helps to make the ISIS results more directly relevant to heterogeneous clinical practice worldwide. Hence, ISIS-4 will provide good evidence about the effects of adding oral controlled-release mononitrate, oral captopril, and intravenous magnesium to current standard treatment.

## SIZE OF DIFFERENCE TO BE MEASURABLE: 10–20 DEATHS PER 1,000

**Reliable assessment of the effects of controlled-release mononitrate, of captopril, and of magnesium on mortality may require some tens of thousands of randomized patients:** The routine use of antiplatelet and fibrinolytic therapies in suspected acute MI has produced a substantial reduction in mortality in many coronary care units. In ISIS-4, fibrinolytic and antiplatelet therapies are likely to be used widely, so the 1-month mortality will probably be only about 8%. Systematic overviews of the results of previous trials of nitrates and of magnesium suggest that these treatments may reduce mortality by at least 15–20%. No such information is yet available for ACE inhibitors, but the promising effects seen on ventricular function, which is importantly related to prognosis,[19] suggest that captopril may reduce mortality by a similar amount. Although a study involving 20,000 patients might well be sufficient to detect effects of this size, it might well not be (whereas a trial twice as large definitely would be). For example, a 15% difference in a trial of 20,000 patients (e.g., 830 deaths among 10,000 controls and 700 among 10,000 treated patients) would be statistically significant ($2p < 0.001$). Even if treatment really does reduce the risk by 15%, however, the play of chance could well make the observed difference in a trial of 20,000 patients somewhat less extreme and hence not conventionally significant (e.g., 800 vs 730 deaths, difference not significant).

Given the wide relevance of the questions being addressed in ISIS-4, this chance of failing to recognize a treatment that really does reduce mortality by 15% is not a reasonable risk to take. The aim in ISIS-4, therefore, is to randomize at least 30,000–40,000 patients to ensure that the risk of such a false-negative result is completely negligible. Of course, if some of the differences are greater than 15%, then the trial is likely to yield statistically definite results for one or more of the comparisons before its scheduled end. That particular comparison would then be stopped early so that later patients in ISIS-4 and elsewhere could benefit. In planning the size of ISIS-4, however, it is not sensible to let over-optimism lead to failure to recognize more moderate mortality differences, since these could still be medically worthwhile with such simple and inexpensive treatments.

**Full efficiency: the ISIS-4 factorial design allows the separate assessment of more than one treatment without any material effect on study size requirements:** In ISIS-4, patients will be randomized between controlled-release mononitrate versus placebo, captopril versus placebo, and magnesium versus open control in a 2 × 2 × 2 factorial design. If, as is hoped, a total of about 40,000 patients are randomized, then there will be about 5,000 patients in each of the 8 possible combinations of trial treatment. Group sizes of 5,000 may not be large enough to yield statistically reliable results, so it may at first sight appear that this factorial design needs far more patients than would have been needed by a simpler design that randomized only one treatment comparison. This is not the case, however, because the way in which the results from such a factorial design can be analyzed allows each question to be answered about as reliably as if the other questions were not being asked (as in ISIS-2 for streptokinase and aspirin[18]; see "Analysis" below).

## ELIGIBILITY: HIGH-RISK AS WELL AS LOW-RISK PATIENTS

**Simple eligibility: high or low risk, suspected or definite acute MI, onset $\leq 24$ hours prior, no clear indications for, or clear contraindications to, trial treatments:** All patients, both high and low risk, are eligible if, in the view of the responsible physician:

- there are considered to be signs or symptoms suggestive of suspected or definite acute MI (with or without electrocardiographic changes);
- the patient is within 24 hours of the onset of the episode of pain (or, if no pain, of other symptoms) that led to trial entry; and
- there are considered to be no clear indications for, or clear contraindications to, any one of the trial treatments—magnesium, ACE inhibitor, or nitrate.

  (The only exception is that patients who are to be given intravenous or other non-trial nitrate for just a few days can still be entered.)

The intent is to randomize patients as promptly as possible after admission to the hospital. If the patient is not considered to be eligible on admission because of some contraindication, the patient should be reassessed a few hours later and may then be eligible if trial treatments are no longer thought to be contraindicated and if it is still within 24 hours of pain onset. (A patient can only be entered once into ISIS-4.)

**Contraindications are specified not by the protocol but by the responsible physician:** The fundamental entry criterion is that the responsible physician considers there to be no clear indications for, or clear contraindications to, any one of the trial treatments. Reasons for not entering patients in the trial are specified not by the protocol but by the responsible physician and might include only a small likelihood of worthwhile benefit, such as:

- negligibly low risk of MI death (e.g., unconvincing history and normal electrocardiogram);
- some major life-threatening disease other than acute MI;

*or* a high risk of adverse effects of trial treatment, such as:

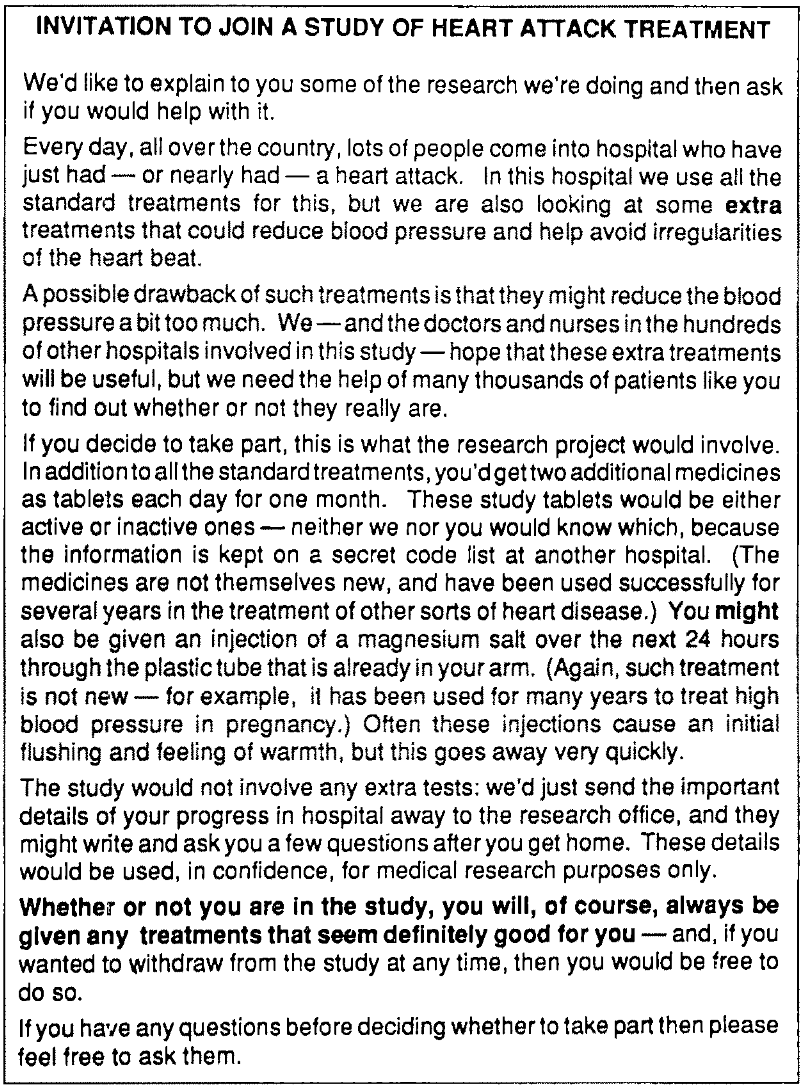
- severely decreased blood pressure—cardiogenic shock or severe hypotension (e.g., systolic blood pressure persistently <90–100 mm Hg, especially with right ventricular infarction or poor peripheral perfusion);
- severely decreased plasma volume—clinical evidence of severe fluid depletion, perhaps due to chronic diuretic use.

(Heart block is not necessarily a contraindication, even though conduction can be slowed by increasing plasma magnesium.)

**Any consent required should be sought before randomization:** Patients who are experiencing the onset of a heart attack are likely to be frightened and may be in severe pain and/or heavily sedated, and trial treatments may be more effective the sooner they are started. In such circumstances, it may not be considered appropriate to delay the start of treatment by discussing the various treatment options in prolonged detail. The degree and timing of consent is, therefore, left entirely to individual doctors to decide for individual patients, in the light of local requirements and advice from any relevant ethical committees. This may result in a wide range of practices, from, at one extreme, formal written consent (e.g., see Figure 2, copies of which are supplied in ISIS-4 trial folders), through various degrees of verbal consent, to, at the opposite extreme, some mention of the trial intended just to offer patients an easy opportunity to initiate any discussion they may want.

## OUTLINE OF PRACTICAL PROCEDURES

**ISIS-4 "log" of all patients admitted to the coronary care unit with acute ischemic heart disease:** All patients admitted to the coronary care unit (or equivalent) with a diagnosis of suspected or definite acute ischemic heart disease should be considered for the trial, and a note made



INVITATION TO JOIN A STUDY OF HEART ATTACK TREATMENT

We'd like to explain to you some of the research we're doing and then ask if you would help with it.

Every day, all over the country, lots of people come into hospital who have just had — or nearly had — a heart attack. In this hospital we use all the standard treatments for this, but we are also looking at some **extra** treatments that could reduce blood pressure and help avoid irregularities of the heart beat.

A possible drawback of such treatments is that they might reduce the blood pressure a bit too much. We — and the doctors and nurses in the hundreds of other hospitals involved in this study — hope that these extra treatments will be useful, but we need the help of many thousands of patients like you to find out whether or not they really are.

If you decide to take part, this is what the research project would involve. In addition to all the standard treatments, you'd get two additional medicines as tablets each day for one month. These study tablets would be either active or inactive ones — neither we nor you would know which, because the information is kept on a secret code list at another hospital. (The medicines are not themselves new, and have been used successfully for several years in the treatment of other sorts of heart disease.) You **might** also be given an injection of a magnesium salt over the next 24 hours through the plastic tube that is already in your arm. (Again, such treatment is not new — for example, it has been used for many years to treat high blood pressure in pregnancy.) Often these injections cause an initial flushing and feeling of warmth, but this goes away very quickly.

The study would not involve any extra tests: we'd just send the important details of your progress in hospital away to the research office, and they might write and ask you a few questions after you get home. These details would be used, in confidence, for medical research purposes only.

**Whether or not you are in the study, you will, of course, always be given any treatments that seem definitely good for you** — and, if you wanted to withdraw from the study at any time, then you would be free to do so.

If you have any questions before deciding whether to take part then please feel free to ask them.

**FIGURE 2. Example of possible consent/information sheet (if required; this is a United Kingdom version) to be read by, or to, patient or relative (and, if so desired, left with the patient afterwards). In the setting of an acute myocardial infarction—when patients are likely to be frightened, in severe pain and/or heavily sedated, and when any appreciable delay may cause some extra deaths—it may not always be considered appropriate to discuss at much length the various options for treatment. In the Fourth International Study of Infarct Survival (ISIS-4), therefore, the degree and timing of consent is left entirely to individual doctors to decide for individual patients, in the light of local requirements and advice from any relevant ethical committees. Copies of this consent/information sheet are supplied to all collaborating hospitals in the ISIS-4 trial folders and further copies are sent on request to collaborating hospitals by the coordinating center.**

for each in the ISIS-4 log (Figure 3), either of the treatment pack number allocated at randomization, or of the main reasons for not randomizing (e.g., not MI; >24 hours; some contraindication). The top copies of all completed and partially completed sheets in the ISIS-4 log will be requested regularly.

**Telephone randomization: ISIS-4 notepads help to make this quicker and easier:** No entry form is needed for ISIS-4, and no special tests have to be done. Patients are entered into the trial by means of a free direct-dial telephone call to a 24-hour randomization service to answer a few questions about the patient. The telephone call may be quicker and easier if the ISIS-4 randomization notepads (Figure 4) are used to prepare for the questions.

At the end of the telephone call, after all the prerandomization details have been provided, the randomization service allocates the patient a specific treatment pack number. All patients who are allocated a treatment pack number are then irrevocably in the trial (whether or not they should have been entered and whether or not they actually receive the allocated trial treatments, since the principal analyses will be by "intention-to-treat"[20]). The treatment pack labeled with this number should then be obtained from the ISIS case that is held in the coronary care unit.

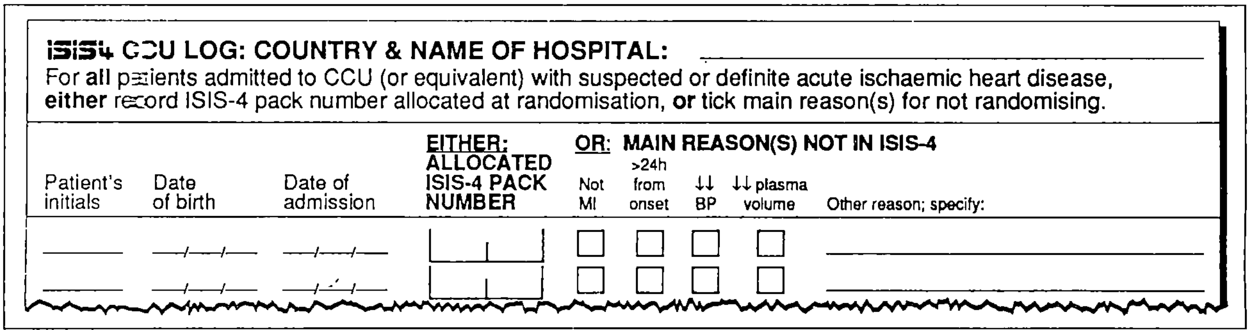
**Trial treatment packs containing study materials and treatment instructions: Controlled-release mononitrate/placebo; captopril/placebo; magnesium/nothing:** Trial treatment should generally be started immediately after starting any antiplatelet therapy and after the early lytic phase (i.e., the first hour or so) of any fibrinolytic therapy. Specific instructions for the trial treatments allocated to that patient (which will differ slightly, depending on whether the patient is allocated to receive magnesium or not) are enclosed in the treatment pack (Figure 5).

The individual treatment pack contains a 1-month calendar-packed (Figure 6) supply of controlled release mononitrate (or placebo) tablets and of captopril (or placebo) tablets, and, if allocated magnesium, two ampules (but no ampules, if allocated to open control).

**Routine management at the discretion of the responsible physician:** Unless clear contraindications develop, the trial treatments should be given as specified, and varied only if the responsible physician believes there is a definite need to do so. All other aspects of patient management are entirely at the discretion of the patient's own doctors. Patients are managed in whatever way appears best for them, with no special treatments, no special investigations, no delay of discharge, and no extra follow-up visits required for the trial. If desired, the patient's family doctor can be written to (perhaps by using, or modifying, the standard letter that is supplied in ISIS-4 trial folders) during the hospital admission or at discharge. This is to inform them about the trial, to request that trial treatment be continued unless it is considered to have become clearly contraindicated, and to ask that they contact the collaborating physician if there are any serious problems. (Similar information is, however, already printed on the trial calendar pack. See Figure 6.)

**No additional investigations and no extra follow-up:** The information routinely recorded in the normal clinical notes (with no special extra records or investigations) should be sufficient for completion of the 1 page discharge form (see Figure 7: this simple list of questions is to be completed just once for each patient after discharge, or prior death, and sent to the national coordinator using the preaddressed envelopes supplied). The discharge forms are printed on duplicating paper so that a copy is automatically produced for the hospital records; these are supplied in the ISIS-4 trial folders.

Postdischarge follow-up is only of mortality, and in most countries (including the United Kingdom)



**ISIS4 CCU LOG: COUNTRY & NAME OF HOSPITAL:** ____________________

For all patients admitted to CCU (or equivalent) with suspected or definite acute ischaemic heart disease, **either** record ISIS-4 pack number allocated at randomisation, **or** tick main reason(s) for not randomising.

| | | | **EITHER:** | **OR: MAIN REASON(S) NOT IN ISIS-4** | | | | |
|---|---|---|---|---|---|---|---|---|
| Patient's initials | Date of birth | Date of admission | **ALLOCATED ISIS-4 PACK NUMBER** | Not MI | >24h from onset | ↓↓ BP | ↓↓ plasma volume | Other reason; specify: |
| ______ | __/__/__ | __/__/__ | | ☐ | ☐ | ☐ | ☐ | ____________ |
| ______ | __/__/__ | __/__/__ | | ☐ | ☐ | ☐ | ☐ | ____________ |

**FIGURE 3. Coronary care unit (CCU) log for ISIS-4.**

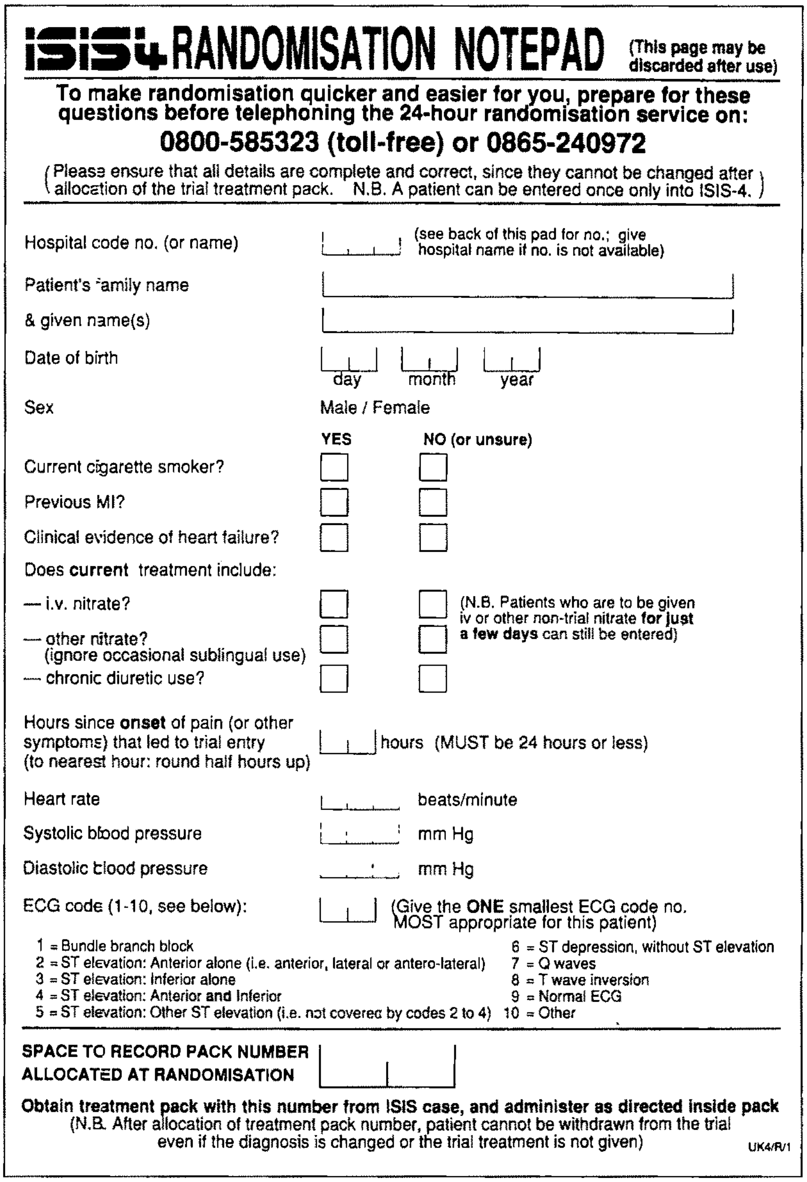
this will not directly involve the hospitals, since it can usually be conducted through central government records.

**Reporting of any serious adverse experiences believed to be due to trial treatment:** To fulfill regulatory authority requirements, serious adverse experiences that are believed with a reasonable probability to be due to trial treatment and that are observed in the hospital or reported to collaborators after discharge should be reported immediately by telephoning the 24-hour randomization service, where a few brief details (i.e., hospital, patient name, nature of event) will be recorded. For the purposes of this study, the only adverse experiences that need to be reported in this way are those that are both serious (i.e., fatal, life-threatening, disabling or significantly delaying discharge), and believed with a reasonable probability to be due to trial treatment. (Following discharge, it may be more difficult to determine whether some serious adverse event is, or is not, due to trial treatment, so such events may need to be reported more readily to the 24-hour randomization service.) It is not required to report in this way those serious side effects or adverse events (including the common modes of death) that are not thought to be due to trial treatment. All such events are, however, routinely recorded on the ISIS-4 discharge form and will be monitored centrally as the trial progresses.

## ANALYSIS

**Main analyses and subsidiary analyses:** The main comparisons will be of:

1. Controlled-release mononitrate versus placebo: Vascular mortality during the first 5 weeks



**ISIS4 RANDOMISATION NOTEPAD** (This page may be discarded after use)

**To make randomisation quicker and easier for you, prepare for these questions before telephoning the 24-hour randomisation service on:**

**0800-585323 (toll-free) or 0865-240972**

(Please ensure that all details are complete and correct, since they cannot be changed after allocation of the trial treatment pack. N.B. A patient can be entered once only into ISIS-4.)

Hospital code no. (or name) ☐☐☐ (see back of this pad for no.; give hospital name if no. is not available)

Patient's family name ☐

& given name(s) ☐

Date of birth ☐☐ day ☐☐ month ☐☐ year

Sex Male / Female

| | YES | NO (or unsure) |
|---|---|---|
| Current cigarette smoker? | ☐ | ☐ |
| Previous MI? | ☐ | ☐ |
| Clinical evidence of heart failure? | ☐ | ☐ |
| Does **current** treatment include: | | |
| — i.v. nitrate? | ☐ | ☐ |
| — other nitrate? (ignore occasional sublingual use) | ☐ | ☐ |
| — chronic diuretic use? | ☐ | ☐ |

(N.B. Patients who are to be given iv or other non-trial nitrate **for just a few days** can still be entered)

Hours since **onset** of pain (or other symptoms) that led to trial entry (to nearest hour: round half hours up) ☐☐ hours (MUST be 24 hours or less)

Heart rate ☐☐☐ beats/minute

Systolic blood pressure ☐☐☐ mm Hg

Diastolic blood pressure ☐☐☐ mm Hg

ECG code (1-10, see below): ☐☐ (Give the **ONE** smallest ECG code no. MOST appropriate for this patient)

1 = Bundle branch block
2 = ST elevation: Anterior alone (i.e. anterior, lateral or antero-lateral)
3 = ST elevation: Inferior alone
4 = ST elevation: Anterior and Inferior
5 = ST elevation: Other ST elevation (i.e. not covered by codes 2 to 4)
6 = ST depression, without ST elevation
7 = Q waves
8 = T wave inversion
9 = Normal ECG
10 = Other

**SPACE TO RECORD PACK NUMBER ALLOCATED AT RANDOMISATION** ☐☐

**Obtain treatment pack with this number from ISIS case, and administer as directed inside pack**
(N.B. After allocation of treatment pack number, patient cannot be withdrawn from the trial even if the diagnosis is changed or the trial treatment is not given)

UK4/R/1

**FIGURE 4. Randomization notepad for ISIS-4.**

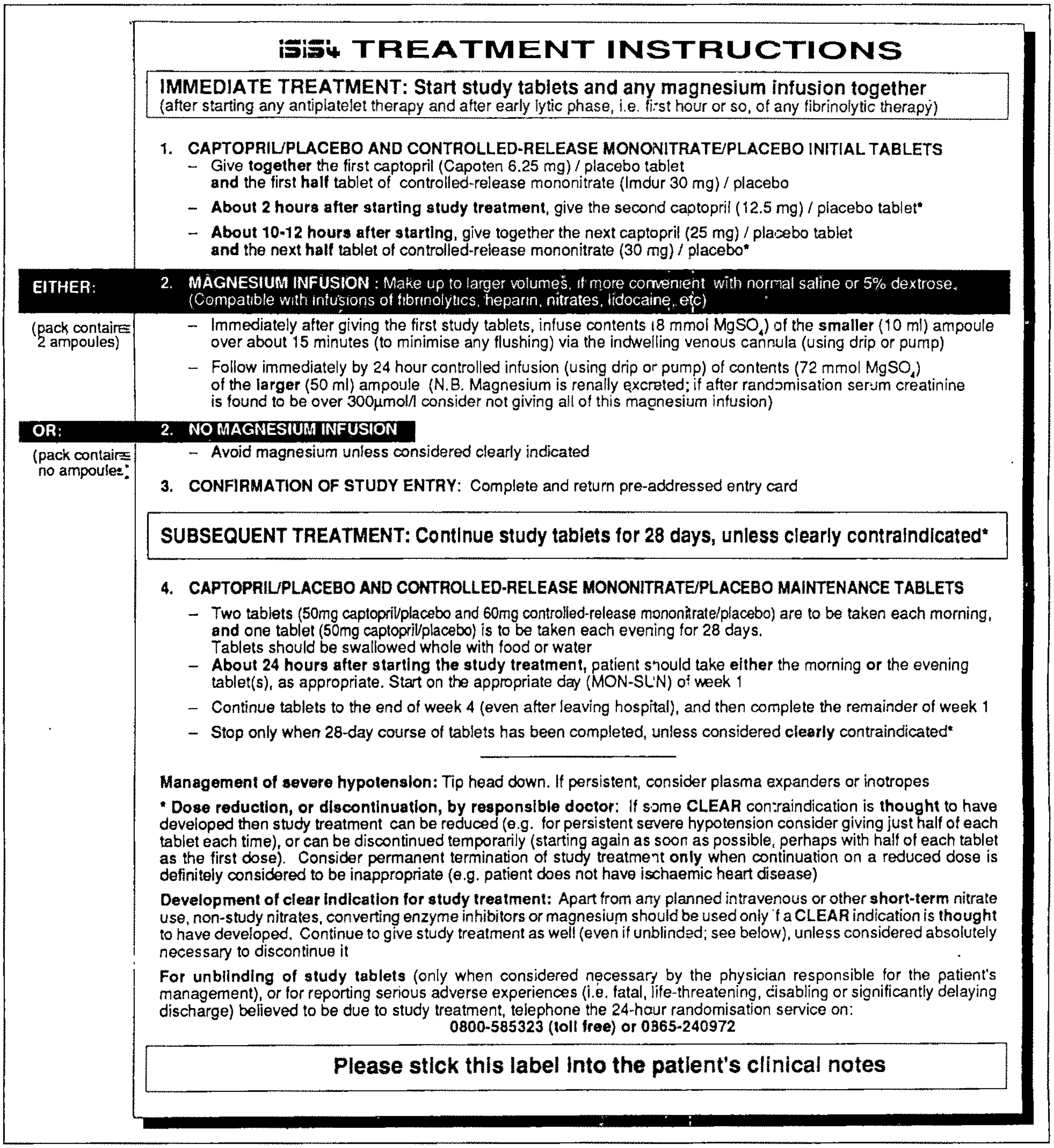
among all those patients allocated active-mononitrate versus all those allocated placebo-mononitrate;

2. Captopril versus placebo: Vascular mortality during the first 5 weeks among all those patients allocated active-captopril versus all those allocated placebo-captopril;

3. Magnesium versus open control: Vascular mortality during the first 5 weeks among all those patients allocated magnesium versus all those allocated open control.

The most important subsidiary comparisons of 5-week vascular mortality involve: (1) comparison of those patients allocated active-mononitrate with those allocated placebo-monotitrate, subdivided by nitrate treatment recorded at randomization; and (2) assessment of whether the group allocated the combination of controlled-release mononitrate and captopril had an outcome that was very significantly different from what might have been expected from the separate effects of the 2 agents.

Although the chief emphasis is on 5-week vascular mortality, all these main and subsidiary analyses will also be repeated for long-term vascular mortal-



## ISIS4 TREATMENT INSTRUCTIONS

**IMMEDIATE TREATMENT: Start study tablets and any magnesium infusion together**
(after starting any antiplatelet therapy and after early lytic phase, i.e. first hour or so, of any fibrinolytic therapy)

1. **CAPTOPRIL/PLACEBO AND CONTROLLED-RELEASE MONONITRATE/PLACEBO INITIAL TABLETS**
   - Give **together** the first captopril (Capoten 6.25 mg) / placebo tablet **and** the first **half** tablet of controlled-release mononitrate (Imdur 30 mg) / placebo
   - **About 2 hours after starting study treatment**, give the second captopril (12.5 mg) / placebo tablet*
   - **About 10-12 hours after starting**, give together the next captopril (25 mg) / placebo tablet **and** the next **half** tablet of controlled-release mononitrate (30 mg) / placebo*

**EITHER:**

(pack contains 2 ampoules)

2. **MAGNESIUM INFUSION** : Make up to larger volumes, if more convenient with normal saline or 5% dextrose. (Compatible with infusions of fibrinolytics, heparin, nitrates, lidocaine, etc)
   - Immediately after giving the first study tablets, infuse contents (8 mmol $MgSO_4$) of the **smaller** (10 ml) ampoule over about 15 minutes (to minimise any flushing) via the indwelling venous cannula (using drip or pump)
   - Follow immediately by 24 hour controlled infusion (using drip or pump) of contents (72 mmol $MgSO_4$) of the **larger** (50 ml) ampoule (N.B. Magnesium is renally excreted; if after randomisation serum creatinine is found to be over 300µmol/l consider not giving all of this magnesium infusion)

**OR:**

(pack contains no ampoules)

2. **NO MAGNESIUM INFUSION**
   - Avoid magnesium unless considered clearly indicated

3. **CONFIRMATION OF STUDY ENTRY:** Complete and return pre-addressed entry card

**SUBSEQUENT TREATMENT: Continue study tablets for 28 days, unless clearly contraindicated***

4. **CAPTOPRIL/PLACEBO AND CONTROLLED-RELEASE MONONITRATE/PLACEBO MAINTENANCE TABLETS**
   - Two tablets (50mg captopril/placebo and 60mg controlled-release mononitrate/placebo) are to be taken each morning, **and** one tablet (50mg captopril/placebo) is to be taken each evening for 28 days. Tablets should be swallowed whole with food or water
   - **About 24 hours after starting the study treatment**, patient should take **either** the morning **or** the evening tablet(s), as appropriate. Start on the appropriate day (MON-SUN) of week 1
   - Continue tablets to the end of week 4 (even after leaving hospital), and then complete the remainder of week 1
   - Stop only when 28-day course of tablets has been completed, unless considered **clearly** contraindicated*

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**Management of severe hypotension:** Tip head down. If persistent, consider plasma expanders or inotropes

* **Dose reduction, or discontinuation, by responsible doctor:** If some **CLEAR** contraindication is **thought** to have developed then study treatment can be reduced (e.g. for persistent severe hypotension consider giving just half of each tablet each time), or can be discontinued temporarily (starting again as soon as possible, perhaps with half of each tablet as the first dose). Consider permanent termination of study treatment **only** when continuation on a reduced dose is definitely considered to be inappropriate (e.g. patient does not have ischaemic heart disease)

**Development of clear indication for study treatment:** Apart from any planned intravenous or other **short-term** nitrate use, non-study nitrates, converting enzyme inhibitors or magnesium should be used only if a **CLEAR** indication is **thought** to have developed. Continue to give study treatment as well (even if unblinded; see below), unless considered absolutely necessary to discontinue it

**For unblinding of study tablets** (only when considered necessary by the physician responsible for the patient's management), or for reporting serious adverse experiences (i.e. fatal, life-threatening, disabling or significantly delaying discharge) believed to be due to study treatment, telephone the 24-hour randomisation service on:
**0800-585323 (toll free) or 0865-240972**

**Please stick this label into the patient's clinical notes**

**FIGURE 5. Treatment Instructions for ISIS-4.**

ity followed up to 5 weeks after the date all randomization into ISIS-4 stops (i.e., all patients will have between 5 weeks and about 18 months of follow-up). In addition, many other exploratory analyses will be performed and presented, often for descriptive purposes, with due allowance made for their exploratory nature. The effects of the trial treatments on total mortality, on particular modes of death, and on various nonfatal events in hospital (e.g., cardiogenic shock, heart failure, cardiac arrest) will also be reported.

**Interim analyses: the data monitoring committee:** During the period of intake to the study, interim analyses of in-hospital mortality and of any other information that is available on major end points (including serious adverse events believed to be due to treatment) will be supplied, in strict confidence, to the chairman of the data monitoring committee, along with any other analyses that the committee may request. In the light of these analyses, the data monitoring committee will advise the chairman of the steering committee if, in their view, the randomized comparisons in ISIS-4 have provided both (1) "proof beyond reasonable doubt"* that for all, or for some, specific types of patients, one particular treatment is clearly indicated or clearly contraindicated in terms of a net difference in mortality, and (2) evidence that might reasonably be expected to influence materially the patient management of the many clinicians who are already aware of the results of the other main trials. The steering committee can then decide whether to modify intake to the study (or to seek extra data). Unless this happens, however, the steering committee, the collaborators, and the central administrative staff (except those who produce the confidential analyses) will remain ignorant of the interim results.

Collaborators, and all others associated with the study, may write through the ISIS trials office to the chairman of the data monitoring committee, drawing attention to any worries they may have about the possibility of particular side effects, or about particular categories of patients requiring special consideration or about any other matters that may be relevant.

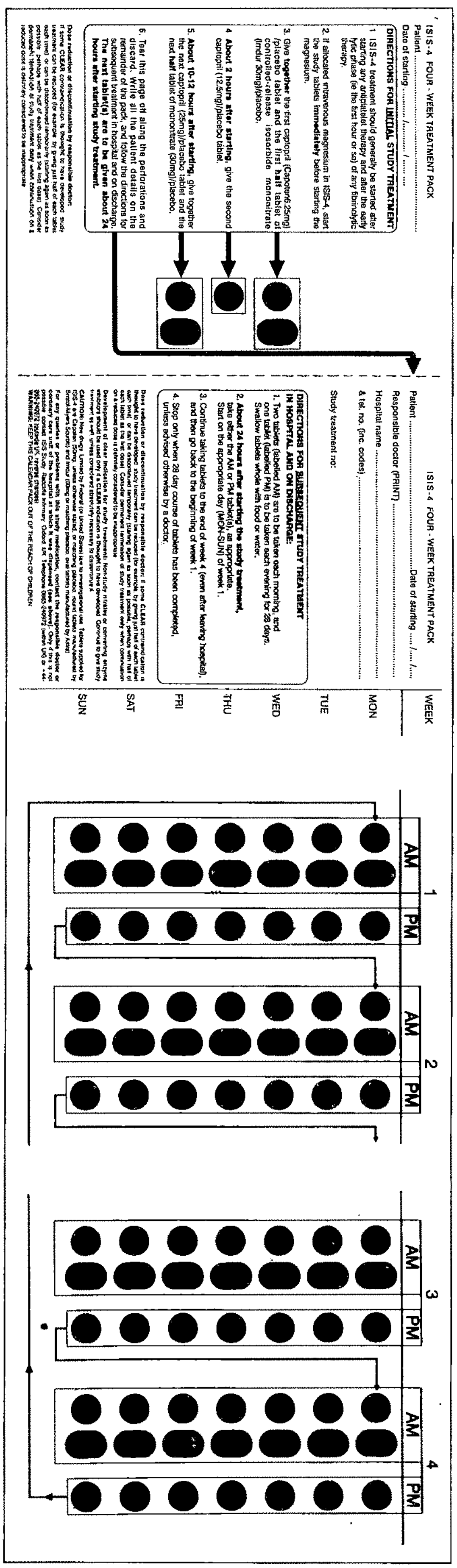
**FIGURE 6. Calendar pack for ISIS-4.**

ISIS-4 FOUR - WEEK TREATMENT PACK
Patient ..................................................
Date of starting ........../........../..........

DIRECTIONS FOR INITIAL STUDY TREATMENT

1 ISIS-4 treatment should generally be started after starting any antiplatelet therapy and after the early lytic phase (ie the first hour or so) of any fibrinolytic therapy.

2. If allocated intravenous magnesium in ISIS-4, start the study tablets **immediately** before starting the magnesium.

3. Give **together** the first captopril (Capoten6.25mg) /placebo tablet and the first **half** tablet of controlled-release isosorbide mononitrate (Imdur 30mg)/placebo.

4 **About 2 hours after starting**, give the second captopril (12.5mg)/placebo tablet.

5. **About 10-12 hours after starting,** give together the next captopril (25mg)/placebo tablet and the next **half** tablet of mononitrate (30mg)/placebo.

6. Tear this page off along the perforations and discard. Write all the patient details on the remainder of the pack, and follow the directions for subsequent treatment in hospital and on discharge. **The next tablet(s) are to be given about 24 hours after starting study treatment.**

**Dose reduction or discontinuation by responsible doctor:**
If some CLEAR contraindication is thought to have developed study treatment can be reduced (for example by giving just half of each tablet each time) or can be discontinued temporarily (starting again as soon as possible, perhaps with half of each tablet as the first dose). Consider permanent termination of study treatment only when continuation on a reduced dose is definitely considered to be inappropriate

ISIS-4 FOUR - WEEK TREATMENT PACK
Patient ..................................................Date of starting ...../...../.....
Responsible doctor (PRINT) ..................................................
Hospital name ..................................................
& tel. no. (inc. codes) ..................................................

Study treatment no:

DIRECTIONS FOR SUBSEQUENT STUDY TREATMENT IN HOSPITAL AND ON DISCHARGE:

1. Two tablets (labelled AM) are to be taken each morning, and one tablet (labelled PM) is to be taken each evening for 28 days. Swallow tablets whole with food or water.
2. **About 24 hours after starting the study treatment,** take either the AM or PM tablet(s), as appropriate. Start on the appropriate day (MON-SUN) of week 1.
3. Continue taking tablets to the end of week 4 (even after leaving hospital), and then go back to the beginning of week 1.
4. Stop only when 28 day course of tablets has been completed, unless advised otherwise by a doctor.

**Dose reduction or discontinuation by responsible doctor:** If some **CLEAR** contraindication is thought to have developed study treatment can be reduced (for example, by giving just half of each tablet each time) or can be discontinued temporarily (starting again as soon as possible, perhaps with half of each tablet as the first dose). Consider permanent termination of study treatment only when continuation on a reduced dose is definitely considered to be inappropriate

**Development of clear indication for study treatment:** Non-study nitrates or converting enzyme inhibitors should be used only if a **CLEAR** indication is thought to have developed. Continue to give study treatment as well, unless considered absolutely necessary to discontinue it.

**CAUTION:** New drugs. Limited by Federal (or United States) law to investigational use. Tablets supplied for ISIS-4 are Capoten (50mg, unless otherwise stated, or matching placebo; round tablets manufactured by Bristol-Myers Squibb) and Imdur (60mg or matching placebo; oval tablets manufactured by Astra)

**For any queries or problems with this study medication, contact the responsible doctor or coronary care unit of the hospital at which it was dispensed (see above).** Only if this is not possible contact ISIS Study, Radcliffe Infirmary, Oxford, UK. Telephone 0865-240972 (within UK) or +44-865-240972 (outside UK, reverse charges)
**WARNING:** KEEP THIS CALENDAR PACK OUT OF THE REACH OF CHILDREN

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*Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but some members of the committee have expressed sympathy with the view that a difference of at least 3 standard deviations in an interim analysis of a major end point may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance,[20] and so no fixed schedule is proposed.

## ISIS4 DISCHARGE FORM: Please complete after patient is first discharged (or prior death) UNITED KINGDOM

**IDENTIFIERS** (please **PRINT**, and give **COMPLETE** details to help us find out about any deaths after discharge)

Hospital name
& code no. of hospital (see back of pad)
Patient's family name
& ALL given names
Maiden name (if appropriate)
Date of birth Day / Month / Year
Address:
House no. & Street
District
Town
County & post-code)
GP's name & address (if available)

**Office use: ISIS i.d. number**
6 1 – ☐☐☐ – ☐☐☐☐ – ☐☐

**OR** patient sticker can be used
to provide some of these details
(although please write in **ANY** details
not given on the sticker )

**DATE OF RANDOMISATION:** Day / Month / Year

**MONONITRATE/PLACEBO TRIAL TABLETS** (tick [✓] one box on EACH line)

YES NO
☐ ☐ First tablet given
☐ ☐ Tablets continued once daily to discharge (or prior death; ignore occasional missed tablet)
☐ ☐ Discharged on controlled-release mononitrate/placebo trial tablets: tick ☐ box if discharged on reduced dose

**CAPTOPRIL/PLACEBO TRIAL TABLETS** (tick [✓] one box on EACH line)

YES NO
☐ ☐ First tablet given
☐ ☐ Tablets continued twice daily to discharge (or prior death; ignore occasional missed tablet)
☐ ☐ Discharged on captopril/placebo trial tablets: tick ☐ box if discharged on reduced dose

**MAGNESIUM** (tick [✓] one box on EACH line, whether magnesium was allocated or not)

YES NO
☐ ☐ Initial bolus infusion (trial or non-trial) given
☐ ☐ 24-hour infusion (trial or non-trial) started
☐ ☐ 24-hour infusion (trial or non-trial) completed

**NON-TRIAL TREATMENT IN HOSPITAL** (tick [✓] one box on EACH line)

YES NO
☐ ☐ Intravenous nitrate
☐ ☐ Other **routine** non-trial nitrate (i.e.ignore occasional sublingual tablet)
☐ ☐ Non-trial converting enzyme inhibitor
☐ ☐ Intravenous beta-blocker
☐ ☐ Fibrinolytic therapy
☐ ☐ Aspirin or other antiplatelet agent
☐ ☐ Antiarrhythmic agent

**Office Use**
☐☐ ☐☐ ☐☐
☐☐ ☐☐ ☐☐

**POSSIBLE SIDE-EFFECTS OF TRIAL TREATMENTS** (tick [✓] one box on EACH line, and enter date any event FIRST occurred)

YES NO Day/Month/Year
☐ ☐ / / Profound blood pressure fall NOT requiring termination of trial medication
☐ ☐ / / Profound blood pressure fall **requiring** termination of trial medication, describe treatment briefly:

☐ ☐ / / Other possible side-effects; describe briefly:

**MAIN EVENTS (FATAL OR NOT) BETWEEN RANDOMISATION AND FIRST DISCHARGE** (tick [✓] one box on EACH line, and enter date any event FIRST occurred)

YES NO Day/Month/Year
☐ ☐ / / Infarction confirmed (e.g. by ECG and/or enzymes)
☐ ☐ / / Reinfarction
☐ ☐ / / Post-infarction angina
☐ ☐ / / Coronary artery bypass graft or angioplasty
☐ ☐ / / Cardiogenic shock
☐ ☐ / / Heart failure requiring treatment
☐ ☐ / / Ventricular fibrillation
☐ ☐ / / Other cardiac arrest
☐ ☐ / / Stroke
☐ ☐ / / Pulmonary or systemic embolism
☐ ☐ / / 2° or 3° heart block
☐ ☐ / / Other serious adverse event(s); describe briefly:
☐ ☐ / / **First discharge alive** from hospital in which patient was randomised
☐ ☐ / / **Death in hospital**, with no prior discharge after randomisation; **and** specify (i) time ____ : ____ (24 hour), **and** (ii) likely **primary** cause of death (tick only **ONE** box, and enclose copy of any available autopsy report):

☐ Arrhythmia ☐ Electromechanical dissociation
☐ Asystole ☐ Reinfarction or extension
☐ Cardiac rupture ☐ Other cardiac/unknown; specify:
☐ Shock ☐ NON-cardiac cause; specify:

**Office Use**
☐☐ ☐☐ ☐☐
☐☐ ☐☐ ☐☐

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**NAME OF PERSON COMPLETING FORM (please PRINT):** ***Thank you***

Please check that **one** YES/NO box has been ticked on **each** line and check that DATES of events are reported, and then send the top copy (no stamp required within UK) to: **ISIS (CTSU), FREEPOST, Radcliffe Infirmary, Oxford OX2 6BR**
**(If ANY relevant question is unanswered this form will be returned, so PLEASE RE-CHECK it carefully!)**

UK4 D.1

**FIGURE 7.**

| | 20,000 allocated MAGNESIUM | | 20,000 allocated CONTROL | Apparent mortality reduction (Magnesium vs. Open control) |
|---|---|---|---|---|
| Row 1 | A 5000 MONONITRATE & MAGNESIUM | vs. | B 5000 MONONITRATE | $D_1$ = Difference in deaths (group B - group A) |
| Row 2 | C 5000 CAPTOPRIL & MAGNESIUM | vs. | D 5000 CAPTOPRIL | $D_2$ = Difference in deaths (group D - group C) |
| Row 3 | E 5000 MONONITRATE & CAPTOPRIL & MAGNESIUM | vs. | F 5000 MONONITRATE & CAPTOPRIL | $D_3$ = Difference in deaths (group F - group E) |
| Row 4 | G 5000 MAGNESIUM | vs. | H 5000 NIL | $D_4$ = Difference in deaths (group H - group G) |

Magnesium versus Open control: Grand total of mortality differences = $D_1 + D_2 + D_3 + D_4$

**FIGURE 8. Planned analyses if ISIS-4 randomizes 40,000 patients. As an example of the appropriate way of analyzing a factorial study, just the planned analyses of the effects of magnesium are described; the analyses of controlled-release mononitrate (Indur) or of captopril (Capoten) would be similar.**

**Planned analyses if ISIS-4 randomizes 40,000 patients:** As an example of the appropriate way of analyzing a factorial study, just the planned analyses of the effects of magnesium are described; the analyses of controlled-release mononitrate or of captopril would be similar. In Figure 8, if magnesium did nothing to mortality in any row, then $D_1$ would differ only randomly from zero, as would $D_2$, $D_3$, and $D_4$. When four things that each differ only randomly from zero are added together, then their grand total will also differ only randomly from zero. Conversely, if the grand total is much more positive than could plausibly be ascribed to the play of chance, this disproves the idea that magnesium does not reduce mortality at all. The grand total of $D_1$, $D_2$, $D_3$, and $D_4$ involves data from all patients, so examination of this total provides about as sensitive a test of whether magnesium saves lives as would a direct analysis of a single trial involving 40,000 patients (and this test does not involve any unjustified comparisons between patients in one row and patients in another row). This argument remains completely valid even though the sizes of any effects of magnesium on mortality may be somewhat different in different rows, for $D_1$ involves only the comparison of like with like, as does $D_2$, $D_3$, and $D_4$: there are no inappropriate direct comparisons of patients in one row with patients in another. This method of analysis of a factorial trial is sometimes referred to as "retrospective stratification"; analogous methods can be used to provide analyses (either of simple two-way trials or of factorial trials) that are retrospectively stratified for age, sex, country, hospital, various patient characteristics, and so on.[20] Although in principle such analyses are preferable, in practice for a trial as large as ISIS-4 they will give results that are virtually identical to those produced by a simple unstratified analysis (see, for example, the ISIS-2 results[18]).

**FIGURE 7. (*Facing page*) Discharge form. Copies of this form, printed on duplicating paper that automatically provides a copy for the patient's clinical notes, are supplied in the ISIS-4 trial folders. Further copies will be sent to collaborating hospitals by the coordinating center as they are required, or on request.**

## ORGANIZATION

### Responsibilities of the chief medical collaborator in each hospital (after local ethical committee approval has been obtained):

1. *To ensure that all medical and nursing staff involved in the care of acute MI are reasonably well informed about the study.* This involves showing the

ISIS-4 training video to the medical and nursing staff in the coronary care unit (and perhaps to some of those in the emergency room), displaying the wall chart in several imaginatively chosen places where it is likely to be read (Figure 9), and distributing the regular newsletters and the plastic protocol summaries (which can be carried in the pockets of the medical and nursing staff). A copy of the video is provided for each hospital so that it can be shown from time to time to new staff.

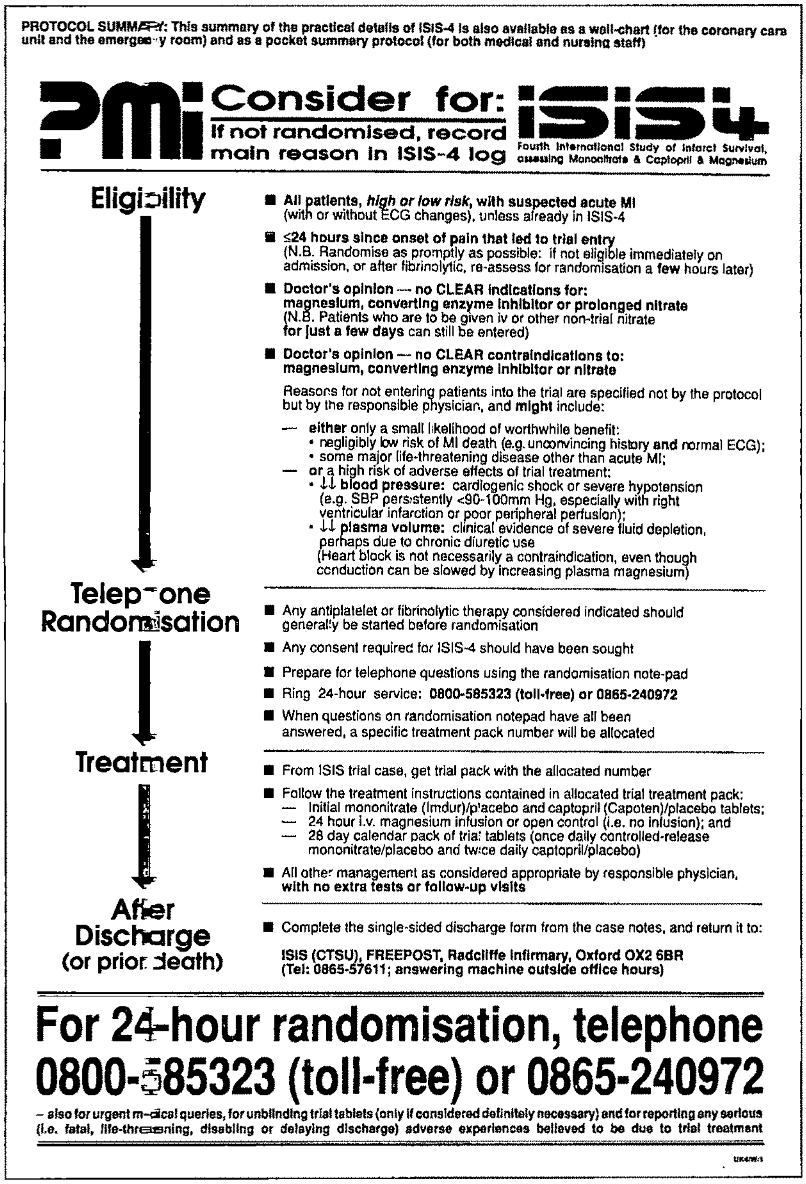
2. *To check the ISIS-4 log routinely* to ensure that virtually all patients admitted with suspected or definite acute ischemic heart disease do get considered for the trial, and that virtually all patients who are eligible, and willing to participate, do get randomized.

3. *To make sure that the single-sided discharge forms are completed reasonably promptly* (e.g., within a month or so of discharge or death in hospital; or, if not, to ensure that they are completed reasonably soon after the reminder to do so arrives), and to telephone the randomization service with details of serious adverse events believed to be due to treatment that are observed in hospital or reported after discharge.

**Responsibilities of the chief nursing collaborator:**

1. *To keep the ISIS-4 log of all patients admitted to the coronary care unit (or equivalent) for suspected or definite acute ischemic heart disease,* with a note either of the treatment pack number allocated at randomization, or of the main reasons for not randomizing.

2. *To ensure that the nurses remind medical staff to consider randomizing all patients with suspected or definite acute ischemic heart disease into ISIS-4.*



**PROTOCOL SUMMARY:** This summary of the practical details of ISIS-4 is also available as a wall-chart (for the coronary care unit and the emergency room) and as a pocket summary protocol (for both medical and nursing staff)

**?MI Consider for: ISIS4**

**If not randomised, record main reason in ISIS-4 log**

Fourth International Study of Infarct Survival, assessing Mononitrate & Captopril & Magnesium

**Eligibility**

- **All patients, *high or low risk*, with suspected acute MI** (with or without ECG changes), unless already in ISIS-4
- **≤24 hours since onset of pain that led to trial entry** (N.B. Randomise as promptly as possible: if not eligible immediately on admission, or after fibrinolytic, re-assess for randomisation a **few** hours later)
- **Doctor's opinion — no CLEAR indications for: magnesium, converting enzyme inhibitor or prolonged nitrate** (N.B. Patients who are to be given iv or other non-trial nitrate **for just a few days** can still be entered)
- **Doctor's opinion — no CLEAR contraindications to: magnesium, converting enzyme inhibitor or nitrate**

Reasons for not entering patients into the trial are specified not by the protocol but by the responsible physician, and **might** include:

— **either** only a small likelihood of worthwhile benefit:
  • negligibly low risk of MI death (e.g. unconvincing history **and** normal ECG);
  • some major life-threatening disease other than acute MI;
— **or** a high risk of adverse effects of trial treatment:
  • ↓↓ **blood pressure:** cardiogenic shock or severe hypotension (e.g. SBP persistently <90-100mm Hg, especially with right ventricular infarction or poor peripheral perfusion);
  • ↓↓ **plasma volume:** clinical evidence of severe fluid depletion, perhaps due to chronic diuretic use
  (Heart block is not necessarily a contraindication, even though conduction can be slowed by increasing plasma magnesium)

**Telephone Randomisation**

- Any antiplatelet or fibrinolytic therapy considered indicated should generally be started before randomisation
- Any consent required for ISIS-4 should have been sought
- Prepare for telephone questions using the randomisation note-pad
- Ring 24-hour service: **0800-585323 (toll-free) or 0865-240972**
- When questions on randomisation notepad have all been answered, a specific treatment pack number will be allocated

**Treatment**

- From ISIS trial case, get trial pack with the allocated number
- Follow the treatment instructions contained in allocated trial treatment pack:
  — Initial mononitrate (Imdur)/placebo and captopril (Capoten)/placebo tablets;
  — 24 hour i.v. magnesium infusion or open control (i.e. no infusion); and
  — 28 day calendar pack of trial tablets (once daily controlled-release mononitrate/placebo and twice daily captopril/placebo)
- All other management as considered appropriate by responsible physician, **with no extra tests or follow-up visits**

**After Discharge (or prior death)**

- Complete the single-sided discharge form from the case notes, and return it to:

**ISIS (CTSU), FREEPOST, Radcliffe Infirmary, Oxford OX2 6BR**
**(Tel: 0865-57611; answering machine outside office hours)**

**For 24-hour randomisation, telephone 0800-585323 (toll-free) or 0865-240972**

**– also for urgent medical queries, for unblinding trial tablets (only if considered definitely necessary) and for reporting any serious (i.e. fatal, life-threatening, disabling or delaying discharge) adverse experiences believed to be due to trial treatment**

UK4W/1

**FIGURE 9. Protocol summary: This summary of the practical details of ISIS-4 is also available as a wall-chart (for the coronary care unit and the emergency room) and as a pocket summary protocol (for both medical and nursing staff).**

Such reminders are of enormous importance: with them the study will succeed and will provide reliable evidence about the value of such treatments both for high-risk and for low-risk patients.

3. *To ensure that the trial treatment packs are readily available, that the nursing staff remember to give all ISIS-4 trial treatments* (unless some contraindication develops), and that the trial entry confirmation card is completed and posted.

**Responsibilities of the national coordinators (after regulatory approval has been obtained):**

1. *To maximize collaboration* and to arrange occasional meetings of collaborators so that any problems or questions can be dealt with.

2. *To provide both medical and nursing collaborators with information about the study's progress* and to deal with most of the problems and questions that might arise.

3. *To represent the collaborators' views* at the steering committee meetings.

**Central coordination: supply of all trial materials, 24-hour randomization service, and data collection and analysis:** The ISIS trials office in Oxford is responsible for providing the specially packed trial cases containing treatment packs, the trial folders containing printed materials, and the ISIS video. These will be supplied, via the national coordinators, to each collaborating center after any relevant ethics committee approval has been obtained. Patient entry in a center can start as soon as the first drug supplies are received. Further supplies will be delivered automatically by the coordinating center, to ensure that patient entry can continue without interruption until the end of the trial. Additional supplies of any printed material can be obtained on request from the national coordinators.

The ISIS trials office is also responsible, in collaboration with the national coordinators, for collection of data (including reports of serious adverse events thought to be due to trial treatment) and for data analyses. The Clinical Trial Service Unit in Oxford provides the 24-hour randomization (and unblinding) service for English-speaking collaborators, with an on-call service for any clinical queries about the trial.

**Finance and non-negligent liability:** The trial is being funded by Bristol-Myers Squibb, who manufacture captopril, and by Astra, who manufacture the controlled-release isosorbide mononitrate. Magnesium sulfate has been donated by Artesan Pharma and Cassella-med, a subsidiary of Hoechst. The general structure of the study was, however, designed independently of these companies, who have no representative in its organization and who will, like the steering committee, remain blind to the results as they accumulate. This arrangement is intended to ensure that no suggestions of lack of objectivity of the findings can be justified. The ISIS trials offer no financial support to the collaborating hospitals, other than reimbursement of any minor costs and provision of free supplies of the trial drugs.

No litigation appears to have arisen from the previous ISIS trials, and it is hoped that none will arise from ISIS-4. If it does, however, the pharmaceutical companies that are participating in the trial will indemnify, and hold harmless, any institution or individual collaborating in ISIS-4 from and against any and all claims or law suits resulting from participation, provided that (1) those seeking indemnity have not departed in any importantly relevant manner from compliance with the protocol and provide all reasonably possible assistance to the pharmaceutical companies in defense of such claims (allowing the companies, if they wish, to settle the claim or take over the defense); and (2) the companies will not be liable for any injuries resulting from medical negligence.

**Publication and ancillary studies:** It may be that certain collaborating centers will want to organize formal additional studies of the effects of the trial treatments on some ISIS patients (e.g., special investigations in selected hospitals). There are no restrictions on this, although it is requested that prior to their start such proposals be referred to the steering committee for discussion.

The success of ISIS-4 depends entirely on the whole-hearted collaboration of a large number of doctors and nurses. For this reason, as in the publication of previous ISIS trials, chief credit for the main results (and for any lives that these save) will be given not to the committees or central organizers, but to all those who have collaborated in the study.

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## APPENDIX

**Steering Committee** (Major organizational and policy decisions): **National Co-ordinators:** Australia: D. Hunt, J. Varigos; Austria: F. Dienstl, P. Lechleitner; Belgium: G. De Backer, M. Kornitzer; Canada: J. Cairns, G. Turpie; Denmark: L. E. Sandos; F. Pedersen; Finland: R. Kala, J. Heikkilä; France: J.-P. Boissel, A. Leizorovicz; Germany: R. Schröder; Greece: N. Karatzas; Ireland: J. Horgan, D. O'Callaghan; Israel: B. Lewis; Netherlands: A. Cohen, R. Koster; New Zealand: H. White, S. MacMahon; Norway: J. Kjekshus, A. Reikvam; Poland: L. Ceremuzynski, A. Budaj; Portugal: R. Seabra-Gomes; South America (ECLA group): E. Paolasso, R. Diaz; Spain: V. Valentin; Sweden: L. Lundkvist, L. Wilhelmsen; Switzerland: T. Moccetti, R. Malacrida, M. Genoni; United Kingdom: M. Flather, A. Pipilis; United States: C. Hennekens, T. Ryan.

**Special Responsibilities:** Chairman: P. Sleight; Coordinator: R. Collins; Statistics: R. Peto, S. Parish; Monitoring other trials: D. Barnett, M. Conway, A. Keech, P. Ridker, K. Woods, S. Yusuf; GISSI liaison: G. Tognoni, M.-G. Franzosi, A. Maggioni; Medical illustration: P. Dove.

**Data Monitoring Committee** (Interim analyses and response to specific concerns): Chairman: R. Doll; Members: P. Armitage, D. Chamberlain, K. Fox, D. Julian, P. Meier, L. Wilhelmsen.

**ISIS Office, Clinical Trial Service Unit** (Supply of materials, collection of data and 24-hour randomization and queries): Clinical: R. Collins, M. Conway, M. Flather, A. Keech, A. Pipilis; Statistical: S. Parish, R. Peto; Administrative: J. Barton, H. Halls, C. Foster, D. Jackson, K. Jayne; Computing: P. Appleby, S. Foster, P. Lloyd; Data entry and secretarial: M. King, G. Mead.

# Early Treatment of Acute Myocardial Infarction with Angiotensin-Converting Enzyme Inhibition: Safety Considerations

Ettore Ambrosioni, MD, Claudio Borghi, MD, and Bruno Magnani, MD, for the SMILE Pilot Study Working Party

**The use of angiotensin-converting enzyme (ACE) inhibitors in acute myocardial infarction (AMI) is based on their capacity to limit ventricular enlargement and dysfunction. To date, the safety profile of administration of ACE inhibitors early in the course of AMI has not been established. In-hospital and long-term consequences of treatment with the ACE inhibitor zofenopril initiated within 24 hours of the onset of symptoms were compared with those of standard treatment in an open-label trial involving 204 patients with AMI who were not undergoing thrombolytic treatment. Zofenopril promptly blocked ACE activation. Blockade was almost complete (91 ± 6%) after 72 hours and paralleled decreases in systolic blood pressure. Systemic blood pressure was acutely reduced by zofenopril, and severe but reversible hypotension occurred in 15% of hospitalized patients and in 3% of those treated over the long term. No adverse clinical or biochemical events were reported during the course of zofenopril therapy. Overall cardiovascular mortality was not significantly reduced by early zofenopril compared with placebo therapy (7.8% vs 10.7% [difference not significant]). The inhospital incidence of acute left ventricular failure and ventricular arrhythmias decreased by 63% and 39%, respectively, among zofenopril-treated patients, who also reported fewer anginal episodes both acutely (68% reduction) and over the long term (56% reduction) and did not require as much drug treatment (i.e., diuretics, digoxin, and/or anti-ischemic agents) during the follow-up phase. Left ventricular size decreased and ejection fraction (EF) increased in patients who received zofenopril, and the improvement was greater among patients with poorer ventricular function (EF < 40%). Early administration of ACE inhibitors may therefore constitute a safe form of therapy for patients with AMI, particularly when the event is complicated by clinical signs or evidence of ventricular dysfunction.**

**(Am J Cardiol 1991;68:101D–110D)**

Angiotensin-converting enzyme (ACE) inhibitors improve the hemodynamic profile of patients with severe congestive heart failure,[1] and sustained therapy has been associated with a reduction in clinical symptoms[2] and prolongation of survival.[3] Since myocardial infarction in its subacute phase shares many of the hemodynamic and humoral features of congestive heart failure, the use of ACE inhibitors was proposed for the treatment of this condition as well.[4] When administered after acute myocardial infarction (AMI), ACE inhibitors have been shown to prevent the progressive deterioration of ventricular function in both animals[5] and humans with depressed ejection fractions.[6,7] Although animal studies have indicated that chronic administration of captopril is associated with prolonged survival,[8] results of patient studies are still limited to improvement in ventricular volume with ACE inhibition, and caution must be exercised in extrapolating these findings to clinical practice. Furthermore, in the studies in patients, captopril therapy was begun during the subacute phase of myocardial infarction, i.e., days to weeks following the event.[6,7] Only limited information is available on the clinical use of ACE inhibitors begun on the first day after the infarction,[9–14] i.e., at the time when these agents could provide additional benefit by improving hemodynamics and reducing activation of the renin–angiotensin–aldosterone system.[15] Table I summarizes the potential clinical benefits and adverse effects of ACE inhibition early in the course of

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From the Institute of Internal Medicine, Service of Clinical Pharmacology, Institute of Cardiology, University of Bologna, Bologna, Italy. A list of SMILE pilot study investigators and associates appears in the Appendix.

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**TABLE I** Potential Clinical Benefits and Adverse Effects of ACE Inhibition Early After Acute Myocardial Infarction

| Benefits | Adverse Effects |
|---|---|
| Reduces blood pressure | Exaggerates pressor effect |
| Prevents development of congestive heart failure | Causes toxicity due to drug overdosage (first dose) |
| Improves exercise tolerance | Exacerbates renal function |
| Limits angina episodes | Reduces end-organ perfusion |
| Limits arrhythmias | Is associated with adverse drug reactions |
| Improves patient survival | Has no impact on outcome |

AMI. An important question is whether the risk–benefit relation in regard to morbidity and mortality is favorable.

Recently, a preliminary assessment of the safety profile and essential clinical and hemodynamic effects of oral administration of an ACE inhibitor was carried out in patients with AMI who were not undergoing thrombolytic treatment.[16] Zofenopril calcium (SQ 26,991), a sulfhydryl-containing ACE inhibitor, is a prodrug–ester analogue of captopril. Its pharmacologic characteristics have been extensively reviewed,[17,18] and the drug seems to have considerable "cardioprotective" properties. It actively inhibits circulating as well as cardiac and vascular converting enzyme, with a substantial capacity to enhance both coronary blood flow[19] and contractile function of stunned myocardium through a mechanism that is independent of prostaglandin synthesis.[20] The present investigation was conducted as a pilot study to assess the safety of zofenopril preliminarily to a larger trial (Survival of Myocardial Infarction Long-term Evaluation [SMILE]) designed to assess the clinical relevance of early ACE inhibition in nonthrombolyzed patients with AMI.

The SMILE pilot experience was conducted as a controlled, multicenter, open-label trial with no constraints on the participating clinicians other than to allocate eligible patients to investigational treatment. This Phase II study was conducted between December 1988 and March 1989 in 16 centers. A total of 204 patients were enrolled according to a common protocol for selection of patients, intervention, concomitant routine therapy, and follow-up. In keeping with the pilot nature of the trial, the research protocol was reviewed by the Ethics Committee of the University of Bologna, which approved the study design, and patients were randomly assigned to receive conventional treatment alone (103 patients) or oral zofenopril calcium in addition to standard therapy (101 patients). Prior to enrollment, informed consent was obtained from each patient and the trial's objectives were fully explained.

Patients were considered eligible if they satisfied the following criteria: (1) the presence of typical chest pain accompanied by ST-segment elevation of ≥0.1 mV in any limb lead and/or ≥0.2 mV in any precordial lead; (2) admission to the coronary care unit within 24 hours of the onset of symptoms; (3) age between 18 and 75 years; and (4) lack of an indication for thrombolytic treatment (late admission to the coronary care unit and/or individual contraindications to fibrinolytic treatment as described in the Gruppo Italiano per lo Studio della Streptokinasi nell'Infarto (GISSI-1) trial.[21] Patients were excluded if there was evidence of cardiogenic shock; persistent hypotension (systolic blood pressure <100 mm Hg); prolonged or traumatic heart massage or tracheal intubation; left bundle branch block; major liver, pulmonary, and/or renal disease; coronary artery bypass within 3 months; serious advanced illness; current treatment with ACE inhibitors; chronic treatment with high doses of diuretics; inability to cooperate; women of child-bearing age; and refusal to provide informed consent. The diagnosis of definite AMI was based on the presence of at least 2 of the following 3 criteria: (1) typical chest pain; (2) appearance of new Q waves with evolving ST or T changes on repeat tracings; and (3) elevation of total serum creatine kinase (and the MB subfraction) to twice the upper limit of normal.

Zofenopril calcium was initially administered by mouth at a dose of 7.5 mg in 2 divided doses and increased to 15 or 30 mg as tolerated according to individual pressor responses. The maximal tolerated dose was then continued for the 12-month period of observation and was not changed after discharge. Recommended treatments for all patients with no specific contraindications consisted of oral aspirin (300–325 mg/day) and intravenous atenolol administered prior to randomization at a dose of 5–10 mg by slow injection and according to First International Study of Infarct Survival (ISIS-1) criteria.[22] In subgroups of patients an estimate of renin–angiotensin–aldosterone activity and invasive assessment of systemic and pulmonary hemodynamics were carried out.

## CLINICAL ASSESSMENT

Demographic, epidemiologic, and biochemical variables were recorded for each patient before randomization, after 1 week, at discharge, and after 1, 6, and 12 months. Systolic and diastolic blood pressures and heart rate were measured at the time of admission and 1, 2, 3, 4, 6, 12, and 24 hours after drug administration during the first day of treatment. Thereafter, pressure measurements were obtained daily prior to dosing up to day 7 and thereafter on scheduled visits during the long-term phase. In addition, during the acute phase of the trial (1–7 days), urinary volume and ventilatory rate were assessed every 6 hours. During the inhospital stay, the presence of congestive heart failure was determined (a) by the presence of 2 or 3 of the following criteria: (1) a third heart sound; (2) bibasilar pulmonary rales; (3) pulmonary congestion on chest radiograph; or (b) exclusively by the need for concomitant treatment with digoxin and/or diuretics. New York Heart Association (NYHA) functional class was used to assess the occurrence of congestive heart failure during the long-term phase. Ambulatory electrocardiography (Holter) monitoring was used in the zofenopril-treated patients at 1, 6, and 12 months to detect ventricular arrhythmias.

Adverse clinical as well as laboratory events were recorded during the acute and the long-term phases of the study. Side effects were reported to a Safety Committee within 48 hours in order to assess the safety profile of the drug during AMI and to protect the patient from any potentially harmful effects of therapy. The finding of >5 *different* severe adverse events not previously reported in comparable clinical studies and judged by the ad hoc committee to be attributable to the study drug, and 3 reports of the same severe adverse event were considered grounds for discontinuing the trial.

## ASSESSMENT OF LEFT VENTRICULAR FUNCTION

Two-dimensional echocardiography was performed at 1 week and after 1, 6, and 12 months of treatment with patients evaluated according to a standardized approach. For the purpose of this study, left ventricular end-systolic and end-diastolic diameters were directly measured, whereas left ventricular ejection fraction was calculated according to Simpson's rule. The echocardiographic recordings for each patient were videotaped, immediately checked for quality, and analyzed at the end of the study period, with all measurements made by the same observer at each center. For central quality control, a randomly selected sample of 25% of all the recordings was reviewed by an experienced and independent observer who was unaware of treatment assignment; the difference between originally reported and control readings was no greater than 4.3% for ventricular diameters and 6.2% for ejection fraction.

In 145 patients, the examination of ventricular diameters was satisfactory both on admission and during the follow-up evaluations, whereas a reliable assessment of ejection fraction was obtained in 108 patients.

The hemodynamic effects of zofenopril were assessed in a subgroup of 10 patients who underwent acute cardiac catheterization to determine mean arterial pressure, right atrial pressure, mean pulmonary artery wedge pressure, cardiac index, stroke volume index, and systemic vascular resistance. Hemodynamic determinations were made 1 hour before and at 0, 1, and 4 hours after the first dose of the drug and then at 12, 24, 36, 48, and 72 hours, in each case immediately before dosing.

The activity of ACE and modifications in the renin–angiotensin–aldosterone system in response to zofenopril were examined in a subgroup of 20 clinically matched patients who were randomly allocated to zofenopril or placebo in addition to conventional treatment. Plasma renin and plasma aldosterone activity were measured by radioimmunoassay, and ACE activity was determined by radioenzymatic assay using an Hyp-Gly-Gly substrate. Plasma samples for humoral determinations were obtained at entry and every 12 hours during the first week of treatment, immediately before the administration of the investigational drug or placebo.

## STATISTICAL CONSIDERATIONS

All data are expressed as means ± standard deviation. Because it was not the purpose of the study to test a statistical hypothesis concerning the relative efficacy of zofenopril and standard treatment, traditional sample-size calculations based on type I errors and power were not carried out. After randomization, each patient was evaluated on an intention-to-treat basis and independently in terms of whether or not the drug was actually given. The chi-square test (with Yates correction when indicated) was used to compare categorical variables, whereas continuous variables were compared by analysis of variance. Analysis of variance for repeated measurements was performed to compare blood pressure values and echocardiographic and hemodynamic findings. A two-tailed Bonferroni *t*-test was employed using the level of 0.05 as the criterion to reject the null hypothesis.

## RESULTS

**Patient data:** A total of 617 consecutive patients with suspected AMI were considered for study and 413 were excluded according to the inclusion/exclusion criteria. The patients in the 2 study groups (zofenopril vs control) were similar in age, gender ratio, clinical history, and interval

**TABLE II** Comparision of Baseline Characteristics of the Two Patient Groups*

| Basline Characteristics | Zofenopril (n = 101) | Control Subjects (n = 103) |
|---|---|---|
| Age (yrs) | 60.7 ± 9 | 61.1 ± 8 |
| Sex (male/female) | 88/14 | 84/18 |
| Clinical history (%) | | |
| Myocardial infarction | 19.8 | 19.6 |
| Angina | 38.6 | 43.9 |
| Hypertension | 32.6 | 35.8 |
| Diabetes | 11.8 | 14.4 |
| Hyperlipidemia | 36.6 | 39.2 |
| Smoker | 56.4 | 55.0 |
| Congestive heart failure | 7.9 | 6.7 |
| Interval between onset of symptoms and drug (hr) | 13.7 ± 6 | 12.4 ± 7 |
| Site of infarct (%) | | |
| Anterior | 30.6 | 33.0 |
| Inferior | 41.5 | 43.6 |
| Lateral | 6.9 | 5.8 |
| Non-Q | 18.8 | 14.7 |
| Total creatine phosphokinase (U/liter) | 934 ± 298 | 978 ± 313 |
| Creatine kinase MB | 117 ± 34 | 106 ± 25 |
| Killip class (%) | | |
| I | 81.2 | 81.8 |
| II | 11.8 | 13.5 |
| III | 4.9 | 3.1 |
| Not defined | 1.0 | 1.6 |

*No statistically significant differences between groups.

between the onset of pain and the concomitant administration of cardiovascular drugs (Table II). No statistical differences between the two groups were found.

**ACE-inhibition and renin–angiotensin–aldosterone response:** Early administration of zofenopril resulted in a 65% inhibition of ACE activity after the first 2 doses of 7.5 mg. Enzyme blockade increased to 85–90% at the higher dose tested (30 mg) and paralleled the decrease in systolic blood pressure (Figure 1) and the extent of the hyperreninemic response (Figure 2). The degree of ACE inhibition detected in control subjects did not exceed 10% and had no effect on blood pressure values, although a significant *decrease* in plasma renin activity occurred with time in these patients (Figures 1 and 2). Plasma aldosterone levels were promptly reduced by zofenopril administration and followed the course of ACE blockade.

**Blood pressure:** Systolic and diastolic blood pressures decreased significantly after 1 week and 1 month in the zofenopril-treated subjects and subsequently returned to baseline levels (Figure 3). The magnitude of pressure reduction was comparable with both doses of zofenopril despite significantly lower values on admission in patients treated with a total dose of 15 mg (systolic 124 vs 136 mm Hg [p <0.005] and diastolic 79 vs 84 mm Hg [p <0.05]). Severe reversible hypotension occurred in 15% of patients given zofenopril and in 6% of control subjects but in only 2 cases did it require discontinuation of the ACE inhibitor and

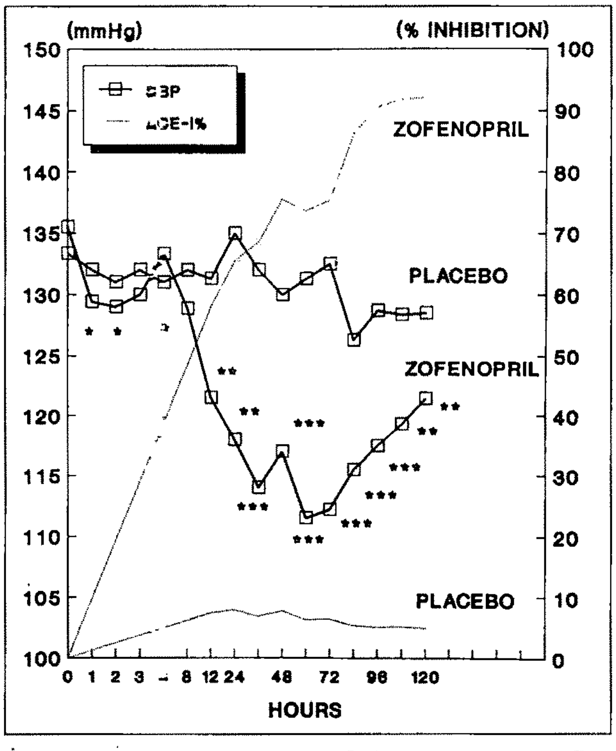


**FIGURE 1. Effects of zofenopril administration on systolic blood pressure (SBP) and angiotensin-converting enzyme inhibition (ACE-I%). *p <0.05; **p <0.01; ***p <0.005 vs placebo.**

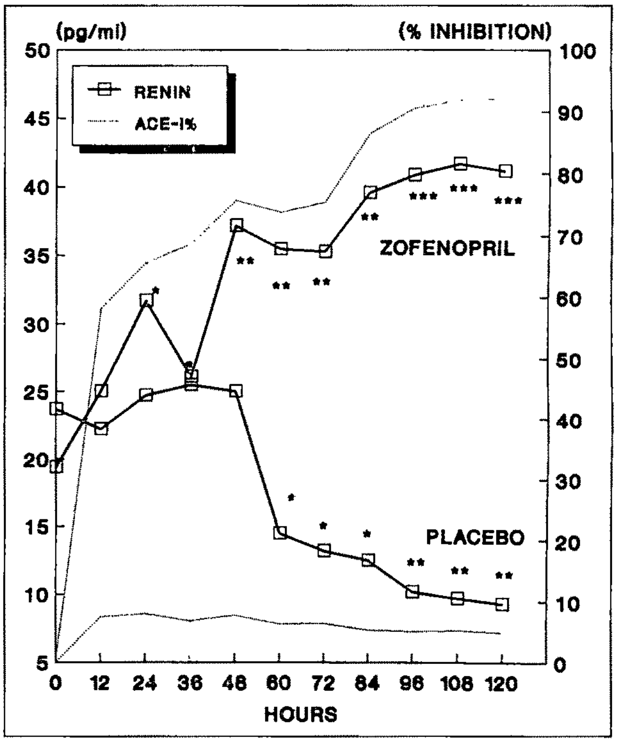


**FIGURE 2. Effects of zofenopril administration on plasma renin activity (RENIN) and angiotensin-converting enzyme inhibitory activity (ACE-I%). *p <0.05; **p <0.01; ***p <0.005.**

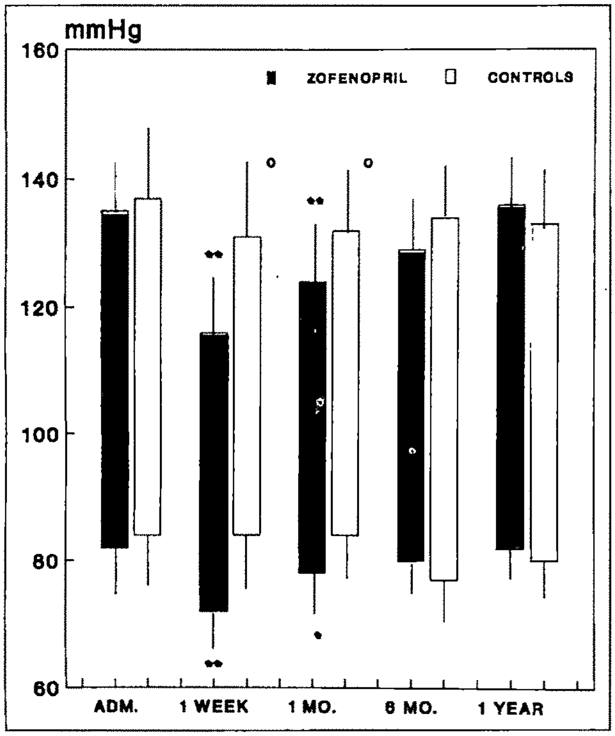


**FIGURE 3. Acute and long-term blood pressure response to zofenopril administration in patients with acute myocardial infarction. ADM = admission.** **$p < 0.05$ vs ADM; °$p < 0.05$ vs control.

specific treatment. Interestingly, the acute pressor response to zofenopril was not affected by the concomitant intravenous administration of nitrates in as many as 70% of patients (Figure 4). During the late (postdischarge) phase, 3% of patients undergoing ACE inhibition experienced symptomatic hypotension, and in them the drug was discontinued.

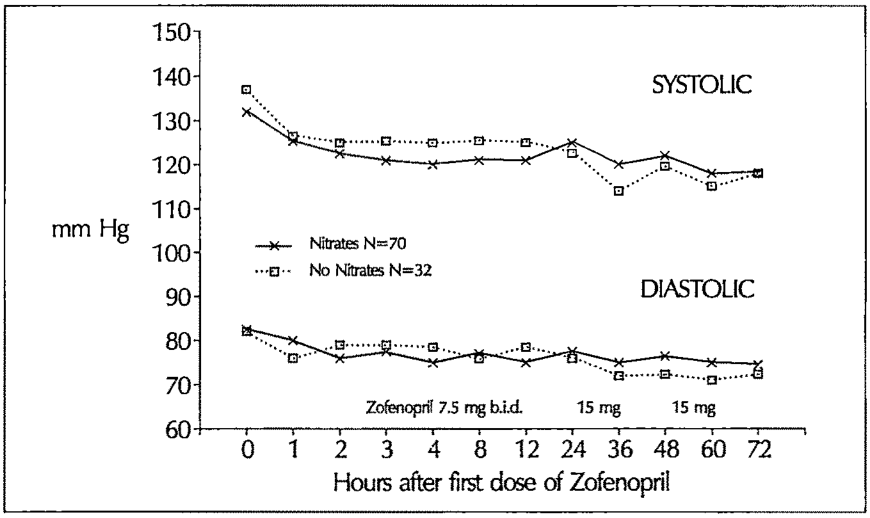
**Echocardiographic changes:** Left ventricular dimensions and ejection fraction improved after 1 month in the zofenopril group and the improvement was maintained at 6 and 12 months of follow-up; no improvement was detectable in the control group (Figure 5). This improvement in echocardiographic parameters was clearly enhanced in patients with baseline ejection fractions below 40% and was not apparent in the subgroup with less severe ventricular compromise (Figure 6).

**Hemodynamic data:** Invasive hemodynamic monitoring demonstrated a significant reduction in mean arterial pressure that was still detectable 1 hour after zofenopril dosing and was sustained for the entire 3 days of observation (Figure 7). The pressure decline occurred along with a dramatic increase in cardiac index and stroke volume index, with no changes in heart rate. Right atrial pressure, pulmonary artery wedge pressure, and systemic vascular resistance decreased progressively, reaching significantly reduced values 36 hours after administration of the initial dose of zofenopril. Interestingly, the hemodynamic improvement was independent of signs of congestive heart failure on admission, even among patients in poorer clinical condition (Figure 8).

**Clinical outcomes:** Cumulative cardiovascular mortality during the 12 months of observation was 7.9% in the zofenopril-treated patients and 10.7% in control subjects, values that were not statistically different. The difference in mortality was attributable mainly to a lower incidence of cardiogenic shock (1 vs 3 patients) and sudden death (2 vs 4 patients) in the zofenopril vs placebo groups. The number of fatal reinfarctions was the same in the 2 groups (2 patients each), as was the incidence of electromechanical dissociation (1 patient each).

The distribution of clinically relevant events recorded in the coronary care unit and during the 12 months of follow-up is summarized in Table III. Anginal episodes were reduced by 18.2% (95% confidence interval [CI] = $-28.7/-7.7\%$ [$p < 0.005$]) during the inhospital phase of the trial in patients

**FIGURE 4. Effects of intravenous nitrate administration on acute (0 to 72 hours) systemic pressor response in patients treated with zofenopril. b.i.d. = twice daily.**



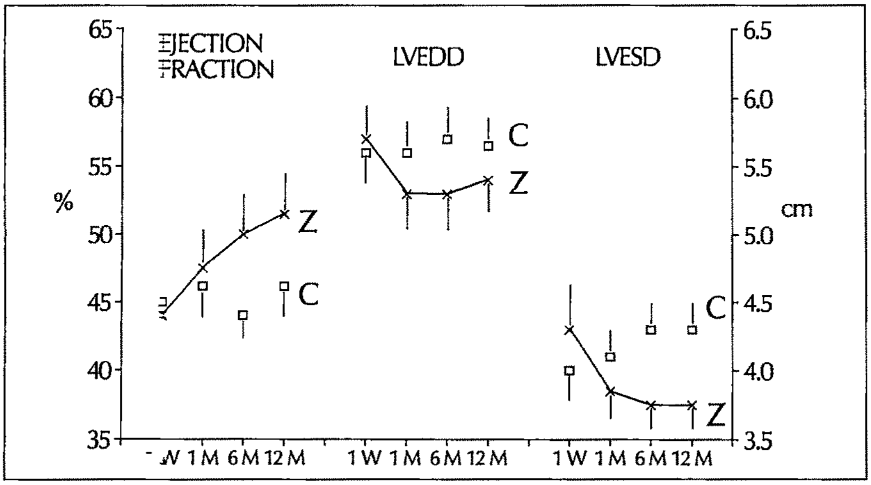


**FIGURE 5. Changes in left ventricular ejection fraction (%) and left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters in patients treated with zofenopril (Z) vs control subjects (C) at 1 week (W) and at 1, 6, and 12 months (M). For ejection fraction measurements there were 53 patients (pz) in the Z group and 55 in the C group. For the dimension measurements there were 71 patients in the Z group and 74 in the C group. *$p < 0.05$; **$p < 0.005$ vs 1 week.**

given the ACE inhibitor and this group had 7.3% fewer episodes of acute congestive heart failure (95% CI = −14.5/−0.1%) and cumulative ventricular arrhythmias of borderline significance (i.e., sustained and nonsustained ventricular tachycardia and ventricular fibrillation) (−11.3%; 95% CI = −21.9/−0.7% [$p < 0.05$]). No differences between the treated patients and control subjects were observed in ventilatory rate and urinary volume during the first 7 days of observation. Aside from angina, which was confirmed to be less frequent in the zofenopril-treated patients after 1 year (−11.9%; 95% CI = −21.9/−1.9 [$p < 0.05$]), no significant differences were noted between the 2 groups of patients with regard to clinical outcome during the follow-up phase of the trial (Table III). The onset of ventricular arrhythmias, as assessed by 24-hour Holter monitoring, was apparently not prevented by zofenopril administration (Table IV) in terms of the rate of ventricular premature beats or the occurrence of sustained and nonsustained ventricular tachycardia.

**Concomitant medication:** The distribution of concomitant cardiovascular drugs in the 2 study groups was well balanced on admission and during the inhospital phase of the trial, indicating the highly satisfactory adherence of the investigators to the protocol (Table V). At the planned 12-month follow-up, the use of oral nitrates and calcium antagonists was significantly greater in the control group, who also exhibited a greater need for digoxin and diuretic therapy.

**Adverse reactions:** No major, unexplained adverse events were reported during either the early or the late phases of the study. Cutaneous rash (2 cases), reversible renal failure (2 cases), proteinuria (2 cases), reversible cough (1 case), and persistent hiccup (1 case) were observed in the zofenopril group. Treatment with zofenopril was not associated with significant changes in the patients' biochemical profiles in the hospital or during the 12 months of observation. In particular, renal function (urea, plasma creatinine, and glomerular filtration rate) remained unchanged, as did

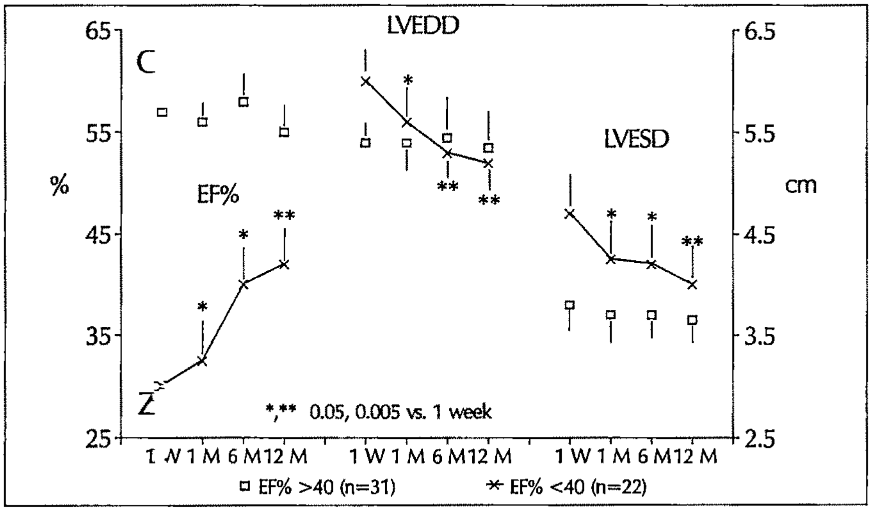


**FIGURE 6. Changes in left ventricular ejection fraction (EF%) and left ventricular end-diastolic (L.V.E.D.D.) and left ventricular end-systolic (L.V.E.S.D.) diameters in patients treated with zofenopril at 1 week (w) and at 1, 6, and 12 months (m). *$p < 0.05$; **0.005 vs 1 week.**

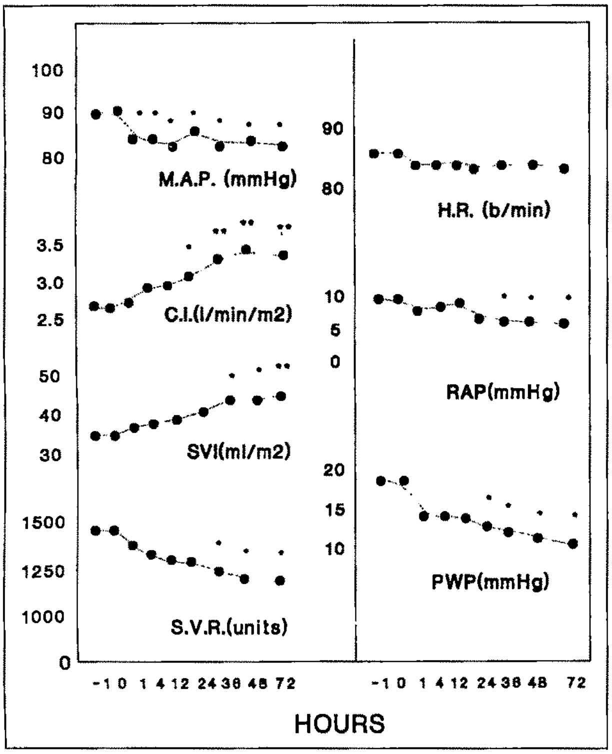


**FIGURE 7. Acute (0 to 72 hours) effects of zofenopril on invasively determined mean arterial pressure (M.A.P.), heart rate (H.R.), cardiac index (C.I.), stroke volume index (SVI), systemic vascular resistance (S.V.R.), right atrial pressure (RAP), and pulmonary wedge pressure (PWP). *p <0.05; **p <0.005 vs 0.**

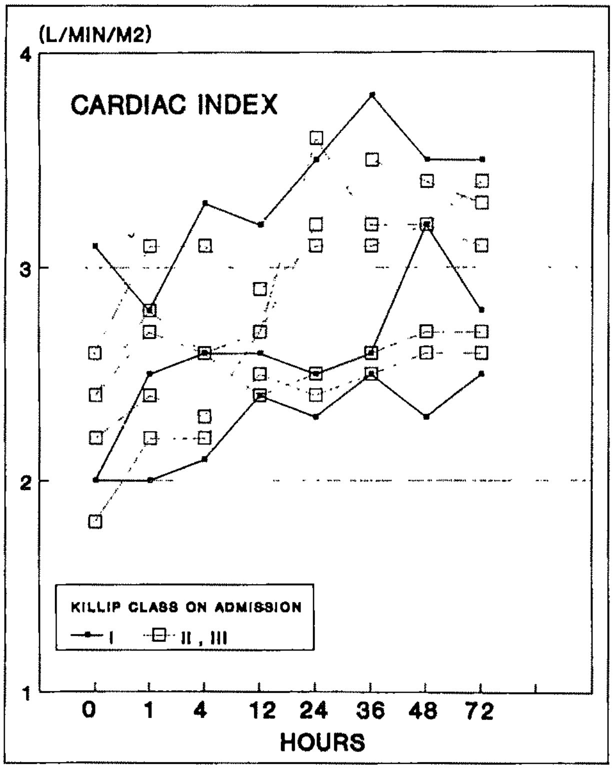


**FIGURE 8. Acute (0 to 72 hours) changes in cardiac index in patients with (Killip class II or III) or without (Killip class I) congestive heart failure on admission who were treated with zofenopril.**

**TABLE III** Major Clinical Events During Inhospital and Long-Term Phases

| | Inhospital (%) | | 12 months (%) | |
|---|---|---|---|---|
| | Zofenopril (n = 101) | Controls (%) (n = 103) | Zofenopril (n = 92) | Controls (n = 91) |
| Angina | 8.9 | 27.1* | 9.8 | 21.7** |
| Reinfarction | 1.9 | 1.9 | 2.1 | 4.3 |
| Congestive heart failure | 3.9 | 11.2† | 2.1 | 3.9 |
| Pericarditis | 7.9 | 8.7 | — | — |
| Ventricular arrhythmias | 11.9 | 23.2† | — | — |
| Coronary artery bypass graft | — | — | 7.5 | 5.5 |
| Percutaneous transluminal coronary angioplasty | — | — | 2.1 | 3.2 |

*p <0.01; †p <0.05.

total plasma proteins, plasma potassium, and white blood cell and platelet counts.

## DISCUSSION

The purpose of this pilot study was to assess the safety and clinical efficacy of early ACE inhibition in patients with AMI who were not undergoing thrombolytic treatment. A significant reduction in acute congestive heart failure, ventricular arrhythmias, and anginal episodes was observed during hospitalization of the zofenopril-treated patients. These patients also showed progressive improvement in ventricular function and less need for digoxin and diuretics during the 12 months of observation, when compared with control subjects. The occurrence of side effects was negligible, and no major adverse reactions were reported during the trial. The potential benefits of ACE inhibition in preventing the progressive deterioration of cardiac function after AMI has been documented in experimental studies in animals[5,23] and supported by data from recent clinical investigations.[6,7,13] The favorable effect of these drugs seems to reside in their ability to maintain cardiac output despite reduced ventricular sizes.[24]

Our preliminary experience with the use of zofenopril early after AMI can be considered favorable. Inhospital cardiovascular mortality in treated patients (4.9%) did not significantly exceed that reported in control subjects in either the present study (6.8%) or previous clinical trials involving comparable populations (range 7.1–9.7%). Further, 1-year mortality was below that reported in GISSI-I in which the mortality was 14.3% for a cohort of patients <75 years of age with uncomplicated infarction who closely resembled our population.[21]

Clearly, the number of patients in our study was too small to allow any statistically significant conclu-

**TABLE IV** Percentage of Patients with Ventricular Arrhythmias During Long-Term Treatment with Oral Zofenopril After Acute Myocardial Infarction: Results of 24-hour Dynamic Electrocardiographic Monitoring

| | 1 Week (n = 94) | 1 Month (n = 90) | 6 Months (n = 84) |
|---|---|---|---|
| VPBs >50/hr | 1.1 | 7.8 | 7.1 |
| Couplets | 12.7 | 22.2 | 18.9 |
| Nonsustained VT | 7.4 | 15.5 | 10.7 |
| Sustained VT | 1.1 | 0.0 | 0.0 |

VPBS = ventricular premature beats; VT = ventricular tachycardia.

**TABLE V** Concomitant Medication During Inhospital and Long-Term Phases

| | Inhospital | | 12 months | |
|---|---|---|---|---|
| | Zofenopril (%) (n = 101) | Controls (%) (n = 103) | Zofenopril (%) (n = 92) | Controls (%) (n = 91) |
| Nitrates | 69.3 | 74.7 | 39.1 | 62.5* |
| Calcium antagonists | 11.8 | 11.6 | 19.5 | 37.3* |
| Beta blockers | 6.9 | 6.8 | 15.4 | 16.5 |
| Antiplatelet agents | 73.2 | 71.8 | 64.3 | 70.3 |
| Diuretics | 9.9 | 12.6 | 11.5 | 23.0* |
| Digoxin | 2.0 | 1.0 | 5.4 | 9.9* |

*p <0.05.

sions to be reached about the ability of zofenopril to reduce postinfarction cardiovascular mortality. However, it was of interest that the early administration of zofenopril was associated with fewer instances of congestive heart failure during the inhospital phase. These findings are well in keeping with animal data[4,23] and human observations with regard to a beneficial role for ACE inhibitors in patients with heart failure complicating AMI.[9,11–14] Moreover, early ACE inhibition was associated with fewer anginal episodes overall, as reflected in the decreased need for nitrates and calcium antagonists during the extended phase of the study. We speculate that these interesting effects in patients with AMI might result from the improvement in ventricular performance achieved with zofenopril therapy, even though a primary anti-ischemic effect of ACE inhibitors due to their coronary vasodilating properties[18,19] has been described in patients with chronic coronary heart disease.[23]

Similarly, the fact that fewer of the treated patients experienced ventricular arrhythmias during their hospitalization could further reflect the overall hemodynamic improvement associated with zofenopril therapy. This interpretation is supported by previous evidence of a reduction in ventricular arrhythmias after contractile performance improved in patients with congestive heart failure who were treated with ACE inhibitors.[3] However, the results of long-term ambulatory monitoring of cardiac rhythm show that zofenopril has no direct suppressive effect on electrical instability (Table IV). Obviously, the role of zofenopril as a primary antiarrhythmic agent early during AMI cannot be ruled out. In an experimental study, Westlin and Mullane[25] reported that the use of ACE inhibitors with sulfhydryl groups (i.e., captopril, zofenopril) can reduce the incidence of ventricular arrhythmias after myocardial reperfusion injury. However, despite these findings, no data are available to prove that ventricular arrhythmias are suppressed by these agents in the absence of reperfusion damage or impairment of ventricular contractility.

In terms of safety, the potential dangers of the use of ACE inhibitors early in the course of AMI is an unpredictable reduction in blood pressure during the acute phase of the disease, when activation of the renin–angiotensin–aldosterone system can vary widely among patients. In this study, the overall percentage of patients with mean arterial pressures <70 mm Hg during the first week of treatment with zofenopril did not exceed 15% (6% in control subjects), and treatment had to be discontinued in only 2% of zofenopril-treated patients (in whom intravenous nitrates were administered simultaneously) because of severe hypotension despite the concomitant intravenous administration of nitrates. Interestingly, the initial hypotensive effect of ACE inhibition was not intensified by the nitrate therapy, and the hypotensive effect gradually diminished during the follow-up, disappearing after 6 months of treatment. These findings contrast with previous reports in which the incidence of severe hypotension ranged from 21% to 50% in patients treated with ACE inhibitors soon after AMI.[9,14,23] However, these earlier studies involved a smaller number of subjects who showed overt signs of congestive heart failure complicating their infarction; thus, they can hardly be compared with the patients in the present investigation.

Since the description by Pfeffer et al[5] of long-term therapy with ACE inhibitors in rats and its favorable effect on the loading conditions of the left ventricle and reduction of progressive ventricular enlargement, many experimental and clinical studies addressing the same issue have reached comparable conclusions.[6,7,13,23] For the most part, the observation that early treatment with zofenopril prevents ventricular enlargement in patients with AMI is largely consistent with previous findings in patients with asymptomatic ventricular dysfunction after myocardial infarction who were studied by either echocardiographic or invasive methodologies.[6,7] However, our observation that the reduction in ventricular dilation is almost complete after 1 month of treatment differs somewhat from the findings of Sharpe et al[7] who reported a diminution of ventricular dilation over 12 months of captopril therapy. Interestingly, the benefit of treatment is apparently limited to patients with lower ejection fractions (Table II) in keeping with available clinical data,[6,7] and appears to be unrelated to infarct location, although the anterior wall is involved in as many as 65% of patients with compromised left ventricular function.

We suggest that hemodynamic and clinical improvement can be achieved by the early administration of ACE inhibitors mainly in patients with poorer ventricular function. The advantage of starting treatment during the acute phase of AMI is that it may promptly prevent the increase in left ventricular volume that can occur even in the absence of overt clinical findings and that can be only partially and progressively limited when treatment is begun during the subacute phase of the disease.

Echocardiographic findings were highly consistent with the hemodynamic changes seen in the subgroup of patients who underwent cardiac catheterization after zofenopril administration. The observed improvement in ventricular function as well as in the systemic and pulmonary hemodynamic profiles matched that reported in the literature for patients who have had congestive heart failure and complications of AMI[9,12,13] and seems to apply to patients without this complication as well, thus confirming the crucial role of early ACE inhibition in preventing deleterious acute left ventricular overloading.

Despite the improved hemodynamic response, the results of the present study did not permit any conclusions about the ability of ACE inhibitors to limit the incidence of congestive heart failure, which was only slightly decreased by ACE inhibition during the 12 months of observation (3.9 vs 2.1% [difference not significant]). This failure can be attributed chiefly to the low rate of congestive heart failure during the first year after AMI, which was estimated not to exceed 6%.[26] In addition, the greater need for digoxin and diuretic therapy among the control subjects (Table IV) could have interfered with the ability to demonstrate a difference between groups of patients evaluated exclusively on the basis of NYHA functional class after 1 year of observation. Obviously, we can draw no firm conclusion about the ability of ACE inhibitors to prevent congestive heart failure, an issue that is being addressed by the Survival and Ventricular Enlargement trial, an ongoing multicenter clinical trial that should provide important data on the clinical consequences of primary treatment of patients with asymptomatic ventricular dysfunction by ACE inhibition.

Zofenopril was well tolerated, and adverse events were few and well within the expected range, with no reports of severe and unexplained adverse events. This is in agreement with previous reports emphasizing the negligible occurrence of untoward effects in patients with hypertension or congestive heart failure chronically treated with ACE inhibitors.[1,2,27] The presence of hemodynamic compromise as well as early administration of the drug in the course of AMI and the effect of concomitant treatment do not seem to modify the safety profile of zofenopril. Its dual route of excretion—hepatic and renal—could represent an important safety feature in patients with AMI.

In conclusion, treatment with zofenopril in patients in the early stage of AMI who are not undergoing thrombolysis can be considered to be reasonable. It appears to be safe and well-tolerated and improves ventricular hemodynamics, both acutely and over the long term, primarily in patients with poorer ventricular function. Unfortunately, the clinical relevance of such treatment could not be assessed by this pilot study; however, it does offer sufficient evidence of benefit to justify a large-scale investigation. SMILE is now enrolling about 2,000 patients with no history of congestive heart failure who are not undergoing thrombolytic treatment. Subjects are randomized to zofenopril or placebo within 24 hours after the onset of symptoms of AMI. SMILE and ISIS-4 should provide important information about the role of early ACE inhibition per se in patients with early AMI.

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## APPENDIX

The SMILE pilot experience was supported through a main grant from Bristol Myers-Squibb Italy, which also provided the drugs.

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# Early Intervention with Angiotensin-Converting Enzyme Inhibitors During Thrombolytic Therapy in Acute Myocardial Infarction: Rationale and Design of Captopril and Thrombolysis Study

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**The adjunctive use of angiotensin-converting enzyme (ACE) inhibitors with thrombolytic therapy early during acute myocardial infarction offers theoretic advantages. In the acute phase, captopril may scavenge free radicals, blunt the catecholamine response, elicit coronary vasodilation, and increase prostacyclin and bradykinin levels. In the chronic phase, ventricular remodeling may be attenuated. At present, a large number of controlled clinical trials mainly focusing on the effects of ACE inhibition in the chronic phase are underway. Only a few studies concentrate on the effect of acute intervention with ACE inhibitors in ischemia–reperfusion, i.e., thrombolysis in myocardial infarction.**

**In April 1990 under auspices of the Interuniversity Cardiology Institute of the Netherlands, a large nationwide acute intervention trial with captopril in 280 patients receiving thrombolytic therapy was started, the Captopril and Thrombolysis Study (CATS). The primary hypothesis of CATS supposes a very early effect of ACE inhibition on evolving myocardial damage due to ischemia and the consequences of early reperfusion. This will be evaluated by serial echocardiography, Holter monitoring and neurohumoral measurements immediately on thrombolysis and during the first year after myocardial infarction.**

**(Am J Cardiol 1991;68:111D–115D)**

It has been established that the renin–angiotensin–aldosterone system is activated following acute myocardial infarction.[1-3] This activation may be associated with serious ventricular arrhythmias,[1] the extension of myocardial damage,[2] and the development of heart failure.[3] Therefore, it was suggested that pharmacologic blockade of the renin–angiotensin system by inhibitors of the angiotensin-converting enzyme (ACE) such as captopril and enalapril may lead to an improvement in the clinical outcome of myocardial infarction.[1-3] Clinical experience has been limited to patients with acute myocardial infarction with symptomatic left ventricular failure.[4-6] Two recent studies demonstrated a beneficial effect of captopril on symptomless ventricular dysfunction after transmural myocardial infarction, but in each case treatment was started between 1 and 6 weeks after the clinical event.[7,8]

Most of the data on the effect of ACE inhibitors in acute myocardial infarction have been derived from animal experiments. These indeed showed beneficial effects,[9,10] but there is still some controversy.[11,12] It has been shown in both the isolated rat heart and a closed-chest pig model that captopril can reduce myocardial damage during reperfusion after myocardial ischemia.[13,14] In the clinical setting, reperfusion can be achieved by early institution of thrombolytic therapy, leading to reduction in infarct size, improvement in myocardial function, and reduction in mortality.[15] However, despite these obvious benefits, many investigators have been debating whether reperfusion itself may sometimes cause myocardial injury, thereby blunting the beneficial effect.[16] Therefore, agents that will minimize myocardial injury following thrombolysis and prevent subsequent increase of infarct size should be investigated.[17]

Furthermore, the process of dilation of the left ventricle in the chronic phase following myocardial

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infarction is an important predictor of patient morbidity and survival. Echocardiographic studies have demonstrated that thinning and dilation of the infarcted myocardium can occur in the clinical situation during the first few months after acute myocardial infarction.[18,19] Infarct expansion may forebear myocardial rupture and aneurysm formation,[20] and ventricular dilation is the most powerful predictor of mortality in patients after acute myocardial infarction, as was shown by White et al.[21]

Two separate studies have demonstrated that treatment with captopril in asymptomatic patients at least 1 week after sustained myocardial infarction and with an ejection fraction of ≤45% can beneficially influence this process of remodeling.[7,8] A reduction in left ventricular dilation was found after 1 year of treatment, leading to improvement of myocardial function. It is only reasonable to assume that eventually survival will also improve, and this was also shown in the experimental model.

Therefore, captopril appears to be very promising as a cardioprotective agent both in the early ischemia reperfusion phase and in the later stages of myocardial infarction. At present, a large number of controlled clinical trials mainly focusing on the effects of ACE inhibition in the chronic phase is underway. Only a few studies have concentrated on the effect of acute intervention with ACE inhibitors in ischemia–reperfusion, i.e., thrombolysis in myocardial infarction.

In April 1990 under auspices of the Interuniversity Cardiology Institute of the Netherlands (ICIN), a large nationwide acute intervention trial with captopril in 280 patients receiving thrombolytic therapy was started, the Captopril and Thrombolysis Study (CATS). The primary hypothesis of CATS supposes a very early effect of ACE inhibition on evolving myocardial damage due to ischemia and the consequences of early reperfusion. This will be evaluated by serial echocardiography, Holter monitoring, and neurohumoral measurements immediately following thrombolysis and during the first year after myocardial infarction.

## CAPTOPRIL AND THROMBOLYSIS PILOT STUDY

In the CATS pilot study, clinical and neurohumoral effects of oral captopril were studied in 57 patients with acute myocardial infarction treated with intravenous streptokinase within 6 hours after onset of symptoms.[22] Patients received either 3 mg or 6.25 mg of captopril orally or no treatment. Captopril was administered within 30 minutes after the start of streptokinase infusion. After both the 3 mg and the 6.25 mg doses, mean arterial pressure decreased significantly. This decrease was comparable with the control group. In an earlier dose-finding study, safety and efficacy of intravenous captopril was investigated. However, all 8 patients receiving intravenous captopril (dose range 0.5–12.5 mg/15 min) showed very profound but short-lasting decreases in mean arterial pressure (from 109 to 45 mm Hg), despite reduction of dose and infusion rate.[23]

Hypotension is frequently observed during thrombolysis by streptokinase alone,[25] as was also noted in the control group of the CATS pilot. Streptokinase promotes the conversion of plasminogen into plasmin, which in turn generates bradykinin from high-molecular-weight kininogen by activating the conversion of prekallikrein into kallikrein.[26] The pronounced decrease in blood pressure after comedication with intravenous captopril may be due to interaction between streptokinase and captopril through potentiation of bradykinin both by streptokinase and captopril.[27]

Interestingly, despite the decrease in blood pressure after captopril, there was no increase in heart rate after either intravenous or oral administration. This is in agreement with the observation that no significant increase of norepinephrine levels occurred after intravenous captopril, despite profound drops in mean arterial pressure. Norepinephrine levels decreased significantly 60 minutes after either 3 mg or 6.25 mg of oral captopril. The finding of decreased norepinephrine levels may be of clinical significance, since it has been suggested that the magnitude of sympatheticoadrenal activation early in the course of clinical acute myocardial infarction is related to the extent of myocardial damage and late mortality.[28] Increased baseline levels of norepinephrine, which have been demonstrated after myocardial infarction,[28–30] were also found in the CATS pilot study before treatment was started. Norepinephrine levels may further increase during thrombolysis and subsequent reperfusion, as was shown in our animal experiments.[13,14] Eventually, this reduction may beneficially influence the clinical outcome of acute myocardial infarction, as shown earlier with β adrenergic blocker treatment.[15]

Recently, Nabel et al[24] reported data on 38 patients treated with recombinant tissue plasminogen activator after the onset of myocardial infarction who were randomized to either intravenous followed by oral captopril or placebo therapy. Exact timing of first dose was not clearly stated but was at least 90 minutes after start of thrombolytic therapy. Compared with the placebo-treated group, the captopril-treated group had significant reductions at day 7 in left ventricular end-diastolic pressure and mean systemic arterial pressure. Although left ventricular ejection fraction did not differ between groups at day 7, left ventricular end-diastolic volume increased significantly in placebo-treated patients but decreased slightly in the captopril-treated group. Although captopril was given intravenously, no significant changes in blood pressure were observed in the acute phase. This underscores that the typical blood pressure response of intravenous captopril during streptokinase is probably directly related to a neurohumoral interaction with streptokinase.

## STUDY DESIGN

CATS enrolled its first patients in April 1990 in 10 academic and nonacademic hospitals (Appendix) in the Netherlands and is projected to include 280 patients by the end of 1991. In April 1991, 170 patients were enrolled. The patient follow-up period is 1 year.

**Patients:** A total of 280 patients presenting with a first anterior myocardial infarction and eligible for thrombolytic therapy (streptokinase, $1.5 \times 10^6$ IU in 30 minutes) within 6 hours after the onset of symptoms will be enrolled. Selection criteria include the presence of characteristic symptoms of acute myocardial infarction and ST-segment elevation of at least 1 mm in leads I and AVL and/or 2-mm ST-segment elevation in 2 or more precordial leads of the 12-lead electrocardiogram, compatible with anterolateral, anteroseptal, and/or anterior wall infarction.

Patients are excluded if using an ACE inhibitor or if severe renal insufficiency (serum creatinine $\geq 300\ \mu\text{mol} \cdot \text{L}^{-1}$), severe hypertension or hypotension (systolic blood pressure $\geq 200$ mm Hg or $\leq 100$ mm Hg; diastolic blood pressure $\geq 120$ mm Hg or $\leq 60$ mm Hg), signs and symptoms of severe heart failure (Killip class III or IV), or serious systemic disease are present, or if contraindications to thrombolytic therapy exist.

**Primary end points:**

1. Left ventricular end-systolic and end-diastolic volumes determined by serial echocardiography within 12 hours after start of study medication and on days 3 and 7 and months 3 and 12.
2. Ventricular arrhythmias, i.e., ventricular tachycardia/fibrillation and accelerated idioventricular rhythm, assessed by ambulatory electrocardiographic monitoring (Holter) during the first 6 hours after admission and during 24 hours after 6 days and after 3 months.
3. Neurohumoral activation [(nor)epinephrine, plasma renin activity] in the acute phase (60 minutes, 12 hours, daily until the 5th day after start of study medication).

**Secondary end points:**

1. Nuclear left ventricular ejection fraction at rest after 3 months;
2. Coronary event rate during follow-up [mortality, reinfarction, development of unstable angina pectoris and the performance of percutaneous transluminal coronary angiography (PTCA) and coronary artery bypass grafting (CABG)];
3. New York Heart Association functional class;
4. Exercise tolerance by serial graded-exercise tests;
5. Infarct size, calculated by computer analysis of serial creatine kinase (CK) and α-hydroxybutyrate dehydrogenase determinations.

**Treatment protocol:** After admission to the coronary care unit, $1.5 \times 10^6$ IU of streptokinase is administered by continuous intravenous infusion during 30 minutes. Nitrates are withheld during the initiation of treatment and are only allowed on specified indication. Double-blind medication is initiated 30 minutes after start of the streptokinase infusion if systolic blood pressure is stable and $\geq 100$ mm Hg. If systolic blood pressure is $< 100$ mm Hg, the initiation of double-blind medication can be delayed for a maximum of 1 hour following start of streptokinase infusion. Initially, an oral dose of 6.25 mg is given, followed by titration as follows: 4 hours: 6.25 mg; 8 hours: 6.25 mg; 16 hours: 12.5 mg; 24 hours: 25 mg.

Dose titration continues if systolic blood pressure, determined immediately prior to the next scheduled dose of study medication, is $\geq 95$ mm Hg. At lower systolic blood pressure, study medication is withheld until the next dosing time.

The target maintenance dose of double-blind study medication is 25 mg three times daily for 12 months. During the 12 months of double-blind therapy, concomitant therapy with calcium antagonists, β blockers, or nitrates will only be instituted for specific indications.

Blood pressure and heart rate are monitored during the first hours with an automatic cuff blood pressure measurement device (Dynamap) with digital printout every 3 minutes during the first hour.

## DISCUSSION

The adjunctive use of ACE inhibitors with thrombolytic therapy early during acute myocardial infarction offers theoretic advantages both in the acute and in the chronic phases. In the early phase, captopril may combine several desirable effects: it can scavenge free radicals, it may blunt the catecholamine response, it can elicit coronary vasodilation and it can stimulate beneficial autacoids such as prostacyclin and bradykinin. Further, in the chronic phase ACE inhibitors may diminish left ventricular volume, prevent ventricular dilation, and improve patient survival. The CATS pilot has shown that at least part of these advantageous effects in the acute phase are demonstrable in the clinical setting of myocardial infarction followed by reperfusion.[22]

At present, a large number of controlled clinical trials investigating the possible beneficial role of ACE inhibitors in acute myocardial infarction are being performed. The number of patients who will be included in these trials is estimated to be more than 75,000. Therefore, many of the questions related to this interesting topic may be resolved in the next 2 years. The hypothesis on which most of these studies are based supposes that the consequences of myocardial infarction, including remodeling and neurohumoral activation, may be blunted by ACE inhibition. At present, it is not clear which patients will benefit most from this intervention and, second, what is the most appropriate moment to start treatment. Most trials underway should be regarded more as secondary prevention trials rather than acute intervention trials. The primary hypothesis of CATS supposes a very early effect of ACE inhibition on evolving myocardial damage due to ischemia and the consequences of early reperfusion. Therefore, the results of CATS may be of paramount importance because its outcome may provide complementary information to the large secondary prevention trials, such as the Survival and Ventricular Enlargement (SAVE) study.

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## APPENDIX

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# Serial Changes in Left Ventricular Size After Acute Myocardial Infarction

Georg Ertl, MD, Peter Gaudron, MD, Christoph Eilles, MD, and Kurt Kochsiek, MD

**The prognosis is poor for patients with left ventricular enlargement associated with large infarcts. We studied 78 patients using gated single-photon emission computed tomography (SPECT, to assess left ventricular volumes), right heart catheterization (to measure pulmonary wedge pressure and cardiac output), and conventional planar radionuclide ventriculography (to estimate ejection fraction), 2–6 days, 3–5 weeks, and 5–8 months after their first myocardial infarction. Patients were assigned to a large or small infarct-size group based on creatine kinase analysis. In 37 patients with large infarcts, left ventricular volume increased and was >27% after 5–8 months than after 2–6 days ($p < 0.05$). Although ejection fraction remained significantly depressed, stroke volume, which initially declined, was restored as a result of dilation and thus returned to normal by 3–5 weeks, indicating that enlargement of the left ventricle compensated for the loss of contractile myocardium and depression of global ejection fraction. The progressive nature of left ventricular dilation suggested that this process is of major pathophysiologic importance and that it plays an etiologic role in the genesis of heart failure and perhaps of sudden death following myocardial infarction. Dilation preceded hemodynamic deterioration, which became evident on exercise after 5–8 months in patients with large infarcts.**

**(Am J Cardiol 1991;68:116D–120D)**

Forty years ago, Linzbach[1] described changes in heart volume in various cardiac diseases and using morphologic methods defined their pathophysiologic importance. He described the transition from concentric to eccentric hypertrophy (dilation) of the heart and suggested that beyond a certain point, dilation may not be functionally compensatory in accord with the Frank–Starling concept, but instead represented "plastische Gefugedilatation," i.e., plastic structural dilation. In addition, he suggested that connective tissue played an important role in cardiac dysfunction during structural changes leading to heart failure. Noting the close relation between the incidence of myocardial infarction and left ventricular dilation, Hort,[2] a collaborator of Linzbach, characterized left ventricular volume changes soon after myocardial infarction. He ligated the coronary arteries of rats and found a relation between the duration of survival after coronary occlusion and left ventricular volume. In experiments involving coronary ligation for variable periods of time and subsequent reperfusion, he showed that infarct size depended on the duration of ligation and that left ventricular volume depended on infarct size. He concluded that the mechanism responsible for left ventricular dilation after myocardial infarction was the loss of postmortem contracture of infarcted tissue. Noninfarcted residual tissue was considered not to become dilated.

More recently, in vivo left ventricular dilation has been analyzed and the concept of infarct expansion has been developed.[3] Infarct expansion adversely influences prognosis: The recognition, pathology, and significance of this phenomenon are reviewed in this supplement by Weiss and Shapiro.[4] However, as discussed in several other contributions to this supplement, left ventricular dilation encompasses infarct expansion as well as eccentric and concentric hypertrophy of residual noninfarcted myocardium.[5]

Several studies have consistently demonstrated the prognostic significance of overall heart size or left ventricular size in patients who have had a

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myocardial infarction.[6] Postinfarction prognosis is determined by many factors, including the extent of coronary heart disease, previous myocardial infarction, gender, hypertension, and diabetes.[7,8] More recently, it has been reported that therapy, too, can improve prognosis.[9] In part, the effects of these factors may be manifested by changes in left ventricular volume that ultimately occur after myocardial infarction. However, the fact that determinants of left ventricular function such as ejection fraction or end-systolic volume measured early after a first infarction are strong prognosticators[10] suggests that the extent of the initial insult plays a major role, as shown by Pfeffer in the rat.[11] This is supported by the observation that the extent of the infarct as estimated by creatine kinase (CK) analysis in patients is a strong determinant of long-term survival.[12]

The reasons for the higher mortality among patients with left ventricular dilation after myocardial infarction are not well understood. Data from the Framingham study have shown that heart failure ensues in 14% of patients within 5 years of their infarction (average 2.3% per year) and it is likely that patients with dilated hearts are more prone to this complication than those with normal-sized hearts.[7] Patients with postinfarction heart failure have a particularly poor outcome. Cardiac dilation has been shown to predispose to arrhythmias,[13] and sudden death is prominent in infarct patients with left heart dilation.[14] In fact, White and associates[10] showed that the finding of an enlarged left ventricle 1–2 months after infarction had considerable prognostic value and reported that 70% of cardiac deaths in their patient population were sudden. Thus, the impact of left ventricular dilation on prognosis after myocardial infarction appears not to be related entirely to the clinical syndrome of heart failure.

## SERIAL CHANGES IN LEFT VENTRICULAR VOLUME

Our understanding of the pathophysiologic importance of left ventricular volume after myocardial infarction was greatly enhanced by the observation that ventricular dilation is progressive in nature. In experimental animals and in patients with adverse clinical outcomes, left ventricular volume increases during the chronic phase of myocardial infarction after the healing and scarring processes are complete.[6,11,14] Serial changes in left ventricular size after acute myocardial infarction and their prognostic significance have been studied by Kostuk and associates[14] using plain roentgenography to determine left ventricular size. Later, angiographic assessment showed that even slight changes in volume, i.e., those not detectable on chest radiographs, were of prognostic importance.[10] In addition, thrombolytic therapy,[15–20] nitrates,[21] β adrenergic receptor blockers,[22] and angiotensin-converting enzyme (ACE) inhibitors[23,24] might have altered hemodynamics, left ventricular volume, and prognosis after infarction. More recently, serial changes in left ventricular volume have been evident on planar radionuclide ventriculography or echocardiography 1 day to 1 year after the acute infarction. Although the accuracy of these methods has been questioned, these studies suggest that early and progressive left ventricular dilation occurs commonly in patients with acute myocardial infarction.[25–29] To understand better the process of left ventricular enlargement and its hemodynamic consequences that may ultimately influence mortality, we studied serial changes in left ventricular volume during a 3-year period following acute myocardial infarction. The data for observations up to 6–8 months are presented here.

## METHODS

Patients with clinically, electrocardiographically, and enzymatically confirmed first myocardial infarctions were entered after giving informed consent. Those >70 years of age and those with unstable hemodynamics or arrhythmias present 3–6 days after the infarction were excluded. Serial blood samples were obtained during the first 3 days after infarction to measure CK and estimate infarct size. CK analysis was used to distinguish patients with small versus large infarcts. Coronary and left ventricular angiography was performed 3–5 weeks after the event and the akinetic and dyskinetic segments observed on angiography correlated well with infarct size as estimated by CK analysis.[30]

Left ventricular volume was measured by gated single photon emission computed tomography (GASPECT). This technique has previously been described and compared with left ventricular angiography in patients after myocardial infarction ($n = 44$; $r = 0.97$; $p < 0.001$).[30] In our hands, GASPECT has been superior to echocardiography and conventional radionuclide angiography for measuring left ventricular volumes, especially when regional contraction abnormalities were present.[31] Left ventricular ejection fraction was determined by conventional radionuclide angiography. Pulmonary artery and capillary wedge pressure and cardiac output were measured using Swan-Ganz catheters and a thermodilution technique. We considered it important to measure left ventricular intracavitary volume, ejection fraction, and stroke volume by independent methods, since a major purpose of this study was to clarify the relation between these parameters during left ventricular remodeling. Measurements were completed and analyzed 2–6 days, 3–5 weeks, and 5–8 months after hospital admission for myocardial infarction. Follow-up studies are planned at 18 months and 3 years.

Patients were divided into 2 groups based on infarct size as determined by CK analysis: 39 were considered to have small infarcts and 37, large infarcts. Therapy was not controlled by the study design. There were no differences in gender, age, or therapy between the 2 groups (large and small infarcts) at the time of recruitment, and the incidence of risk factors was similar except that diabetes mellitus was more prevalent in the group with large infarcts. Only a small fraction of patients with large infarcts received ACE inhibitors and digitalis at the time of entry; however, 15% of this group received ACE inhibitors and 31% digitalis during the last 5 to 8 months of the study. No patient had clinical evidence of heart failure.

## RESULTS AND DISCUSSION

Arterial pressure, heart rate, and pulmonary capillary wedge pressures were similar in both groups (patients with large and small infarcts) and did not change over the course of the observations (Table I). Left ventricular ejection fraction was reduced in patients with large infarcts and was significantly lower than in patients with small infarcts both 3–5 weeks and 5–8 months after infarction. However, this variable did not change significantly over time in either group. Left ventricular end-diastolic volumes were normal and similar in patients with large and small infarcts early (2–6 days) after the event. Although left ventricular end-diastolic volume increased progressively in patients with large infarcts, it remained stable and even decreased during the later phase of observation in those with small infarcts. Thus, patients with large infarcts developed significantly larger volumes within 3–5 weeks and increased to 8 months, compared with those who had small infarcts. End-systolic volumes showed a similar increase in patients with large infarcts. Stroke volume was reduced in patients with large infarcts 2–6 days after infarction, but returned to normal by 3–5 weeks after infarction. Stroke volume did not change in the patients with small infarcts at any time. Thus, stroke volume was similar in the patients with small and large infarcts between 3–5 weeks and 5–8 months.

**TABLE I** Hemodynamic and Left Ventricular Volume Measurements in 37 Patients with Large* Myocardial Infarcts

| | Time of Observation | | |
|---|---|---|---|
| | 2–6 days | 3–5 weeks | 5–8 months |
| Mean arterial pressure (mm Hg) | 92 ± 14 | 89 ± 12 | 95 ± 10 |
| Heart rate (beats/min) | 80 ± 11 | 74 ± 13 | 75 ± 10 |
| Pulmonary wedge pressure (mm Hg) | 11 ± 6 | 13 ± 9 | 12 ± 5 |
| LV ejection fraction (%) | 43 ± 2 | 43 ± 2 | 41 ± 3 |
| LV end-diastolic volume index (mL/m$^2$) | 72 ± 3 | 86 ± 5† | 92 ± 5†‡ |
| LV stroke volume index (mL/m$^2$) | 35 ± 2 | 42 ± 2† | 42 ± 2† |

*Defined by an area underneath the creatinine kinase/time curve > 10 U/liter × m$^2$.
†$p < 0.05$ vs 2–6 days.
‡$p < 0.05$ vs 3–5 weeks.

Since stroke volume increased in patients with large infarcts during the early phase of observation, left ventricular dilation can be considered to be a compensatory response to the loss of contractile myocardium and the depressed ejection fraction (Figure 1). The mechanism of this compensatory response is most likely structural dilation of the ventricle, with the geometric advantage provided by the larger volume. The concept of compensatory structural dilation to restore stroke volume is in accordance with various previous studies[25,26,28,29] and with theoretical considerations.[32] However, according to Laplace's law, an increase in ventricular volume results in an increase in wall stress. Although hypertrophy of residual myocardium occurs gradually, most studies show that it is not sufficient to normalize wall stress. Thus, compensatory dilation is associated with the burden of permanently increased wall stress.

In this study we observed the transition from compensatory left ventricular dilation from 2–6 days to 3–5 weeks after myocardial infarction followed by noncompensatory dilation with no further hemodynamic benefit from 3–5 weeks to 5–8 months after infarction. The increase in left ventricular volume from 72 ± 3 to 92 ± 5 ml/m$^2$ (or 27%) seen in about half of our patients during this relatively short period suggests that a major pathophysiologic change occurred. Progressive left ventricular dilation and hemodynamic deterioration occurred only in the patients with large infarcts. However, our definition of "large infarct" was arbitrary. Patients with the most extensive infarcts were probably not included, since they were in cardiogenic shock or heart failure during the early postinfarction phase. Previously, we observed increases in left ventricular volume in patients with moderate as well as with large infarcts, i.e., in two

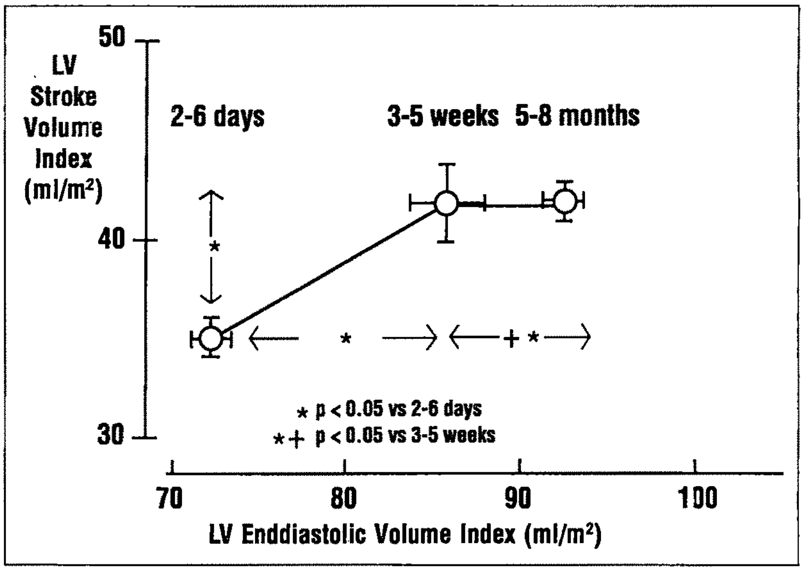

**FIGURE 1. Relation of left ventricular (LV) stroke volume index and end-diastolic volume index in 37 patients 2–6 days, 3–5 weeks, and 5–8 months after a large myocardial infarction. LV end-diastolic volume index increased progressively during the time of observation. LV stroke volume index also increased, suggesting compensatory LV dilation during the early phase (3–5 weeks). The further increase in LV end-diastolic volume was not accompanied by an increase in stroke volume and was therefore considered noncompensatory.**

thirds of all infarct patients, during the 4 weeks following infarction.[30] Recent observations from our laboratory suggest that stroke volume and ejection fraction during exercise are progressively impaired in patients with large infarcts and left ventricular dilation and that wedge pressure increases more during exercise at 5–8 months than at 3–5 weeks after infarction. Thus, although hemodynamics at rest were stable, they clearly deteriorated during exercise.

It is of clinical importance and of potential therapeutic value to analyze the determinants of left ventricular dilation. After infarct size, infarct location was considered to be one of the most important of these determinants. However, on average, patients with anterior infarcts develop larger infarcts and a considerable proportion of patients with inferior infarcts presented with dilation in this and earlier studies.[29] Early reperfusion achieved by thrombolytic therapy may reduce infarct size and thus limit dilation. By changing the physical characteristics of the infarcted tissue, reperfusion itself may influence remodeling, as pointed out by Lamas et al[33] elsewhere in this supplement. This mechanism might explain the effectiveness of late thrombolytic therapy as observed in the Second International Study of Infarct Survival (ISIS-2) trial.[16]

Analysis of data from the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) and other studies suggest a reduction of left ventricular volume by thrombolytic therapy.[15-20] The effect on left ventricular dilation of other factors that affect left ventricular wall stress such as physical activity or β receptor blockade is not well defined, whereas the use of ACE inhibitors have been shown to limit cardiac dilation.[23,24]

## CONCLUSION

Left ventricular dilatation in patients with large infarcts is associated with a poor prognosis. Earlier studies have noted the development of left ventricular enlargement in as many as two thirds of all patients with infarction.[30] Such dilation is progressive in about one third of patients and compensates for the loss of contractile myocardium and depression of global ejection fractions. Although the reduction in ejection fraction persists, stroke volume is restored by this compensatory dilation. However, the progressive nature of such enlargement without further increase in stroke volume suggests that dilation plays a major role in the development of heart failure and perhaps sudden death following myocardial infarction. Dilation precedes hemodynamic deterioration, which becomes evident during exercise after 6–8 months.

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# Influence of Severity of Heart Failure on the Efficacy of Angiotensin-Converting Enzyme Inhibition

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**Angiotensin-converting enzyme (ACE) inhibition slowed the progression of congestive heart failure (CHF) in 170 patients who were randomly assigned to either captopril or placebo in the Munich Mild Heart Failure Trial. The two major end points were progression from New York Heart Association (NYHA) functional classes I, II, or III to class IV, despite optimal, adjusted standard therapy, and death due to CHF. The relative risk for progressive CHF with captopril therapy was 0.34 (95% confidence interval = 0.17–0.68; p = 0.01). A total of 52 prerandomization variables were tested to determine their contribution to disease progression. Logistic regression analysis revealed 5 independent risk factors for progressive CHF: NYHA class, left ventricular end-systolic diameter, need for diuretic, age, and cardiothoracic ratio. The presence of >2 of these risk factors increased the odds ratio for progression to 8.13 (p <0.001) compared with the presence of 0–2 risk factors. However, the effectiveness of captopril in preventing progression was higher within the subgroup of patients who had less severe CHF: the odds ratio was 0.12 (95% confidence interval = 0.03–0.45; p <0.01) for patients in NYHA class I or II on captopril and was 0.83 for those in class III.**

**We conclude that the severity of CHF, as represented by the above-defined risk factors, is directly related to the likelihood for the development of progressive heart failure. However, the less severe the heart failure, the more effective the treatment with captopril will be in preventing disease progression. Thus, ACE inhibition has considerable potential for improving the prognosis of patients with mild heart failure.**

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Although the symptoms of congestive heart failure (CHF) have been well recognized for thousands of years[1] the realization that cardiac dysfunction is the major cause of these symptoms was determined only relatively recently. Since death is much more likely to occur among patients with New York Heart Association (NYHA) class IV heart failure[2–4] than among those with mild heart failure,[5–7] most studies assessing prognosis have focused on reducing mortality,[2,8,9] and few have tried to limit progression of this disease.[10] However, the therapeutic efficacy of angiotensin-converting enzyme (ACE) inhibitors in preventing an increase in left ventricular volume as a potential compensatory mechanism for progressive pump dysfunction after acute myocardial infarction has been demonstrated in 3 trials.[11–13]

The Munich Mild Heart Failure Trial (MHFT) included patients with mild (minimal to moderate) symptoms and tested whether an ACE inhibitor prevented the development of progressive heart failure, as reflected in NYHA functional class IV, as well as death from CHF.[14] This report is concerned with the major parameters that determine the likelihood of disease progression. In addition, we tested whether the efficacy of ACE inhibition is limited to patients with minimal to mild CHF or to those with mild to moderate disease.

## METHODS AND STUDY DESIGN

The MHFT has been described elsewhere,[15] and the study methods have been previously published in detail.[14] Briefly, MHFT constituted a randomized, double-blinded, placebo-controlled, parallel group monocenter trial involving 170 patients with CHF who were in NYHA functional classes I–III while receiving standard therapy. The patients

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were randomly assigned to treatment with either captopril (n = 83) or placebo (n = 87) in addition to diuretics (79%), digitalis (59%), nitrates (59%), and other standard therapy as clinically appropriate. Entrance criteria consisted of slightly modified criteria after McKee et al.[4]

Baseline examination included cardiac and general history, physical examination, laboratory workup, chest radiograph, electrocardiography, echocardiography (when technically feasible), and either radionuclide ventriculography or left ventriculography with cineangiography, as clinically appropriate. Patients in whom the etiology of the underlying cardiac diseases was unclear were excluded. Follow-up examinations using a standardized questionnaire of cardiac complaints were performed at 3-month intervals. The total observation period was 5 years (minimum 3 months, median 2.7 years).

The dose of captopril was 25 mg twice daily, but this was adjusted according to serum creatinine levels.

End points included death due to heart failure, with subclassification into sudden death, and death due to pump failure, as well as progression to severe heart failure (NYHA functional class IV) despite optimal, adjusted concomitant therapy.

**Statistics:** According to the published literature,[4] a mortality of 37.5% at 2.5 years was assumed for the group given placebo. To establish that progressive heart failure or CHF death was reduced to 17.5% as a result of captopril therapy, a sample size of 170 patients was precalculated ($\alpha = 0.05$, $\beta = 0.20$, Fisher's exact 2-tailed test). The 2 treatment groups were compared with regard to the main objective of the study according to the intention-to-treat approach and using the same statistical model as for the sample-size calculation. Further statistical analyses included the calculation of odds ratios for 52 prerandomization variables, regression analysis, and discriminant analysis.

**Informed consent:** Informed consent was obtained from each patient prior to randomization and after detailed written information had been provided.

## RESULTS

**Description of patients and underlying cardiac diseases:** A total of 170 patients (128 males and 42 females) with a median age of 63 years were randomized. In the majority of patients, CHF had been present for between 4 weeks and 12 months. The median observation period was 2.7 years. The most common cause of CHF was coronary artery disease with prior myocardial infarction (in 69%); 20% had dilated cardiomyopathy and 12% had hypertensive heart disease. Most patients had mild clinical symptoms while on therapy (mean and median NYHA functional class II), although many had a history of more severe symptoms earlier. The mean ejection fraction was 35%.

**End points:** *Death:* Twenty-two patients in each group died (25.9%): 81.8% of deaths were due to heart failure, 34.1% to pump failure, and 47.7% to sudden cardiac death. Kaplan-Meier life table 5-year mortality in the placebo group was 40%. "Other cardiovascular" deaths occurred in 13.6% and noncardiovascular deaths constituted 4.5% of all deaths. Eleven of the 22 deaths in the placebo group and 4 of the 22 deaths in the captopril group were due to pump failure (p = 0.10). No differences were found in sudden deaths and in the "other cardiovascular" or noncardiovascular deaths.

*Progression of heart failure to NYHA class IV:* Heart failure progressed in 18.8% of all patients (9 patients in the captopril group vs 23 patients in the placebo group; p = 0.01). Mean survival time without deterioration to NYHA functional class IV within a total observation period of 5 years was increased by 223 days in the captopril-treated group ($p < 0.02$). The risk of disease progression to class IV was higher during the first year following randomization among patients randomized to placebo, and this higher risk persisted beyond the time of observation.

*Total heart failure events:* Total heart failure events (progression of CHF to NYHA functional class IV or death due to CHF) occurred in 19 and 32 patients on captopril and placebo therapy, respectively (p = 0.065). After 1 year, 19% of the patients on captopril and 28% of those on placebo had experienced 1 of these major events; by the end of the study, these percentages were 31% and 42%, respectively (life-table p = 0.07) (Figure 1).

*Determinants of progression of heart failure:* Since the major difference in this study was found in the end point representing progression of CHF, the effect of 52 prerandomization variables on the likelihood of progression was investigated. Odds ratios and p values according to Fisher's exact test (2-tailed) were calculated for each of these 52 parameters. Table I shows all parameters for which the difference between the risk factor was significant ($p < 0.05$). The major determinants of progression of CHF, as shown in Table I, are measures of left ventricular or total heart size and function (cardiothoracic ratio, echocardiographic left ventricular end-diastolic and end-systolic diameters, fractional shortening) and of congestion (need for diuretics, signs of pulmonary congestion on chest radiographs, paroxysmal dyspnea, neck vein distension, pulmonary rales). In addition, tachycardia, inactive lifestyle, NYHA functional classification, and age have been found to be risk factors.

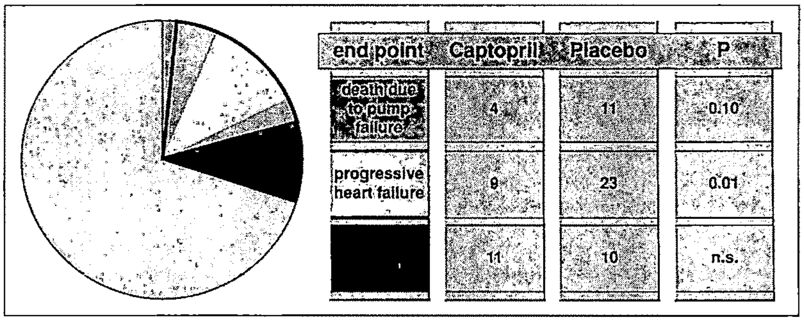
Assuming an interdependency among some of these risk factors, we performed a multivariate logistic regression analysis within 4 categories: general findings, history, physical examination, and laboratory findings. Within each of these 4 categories, the following factors were found to contribute independently to the progression of CHF: *General findings,* NYHA class III and age over 60 years; *history,* inactive lifestyle, need for loop diuretics, nocturia; *physical examination,* neck vein distension and pulmonary rales; and *laboratory findings,* left ventricular end-systolic diameter exceeding 51 mm (on M-mode echocardiography) and cardiothoracic ratio above 50%.

The following were *not* independent contributors to risk for CHF progression. Gender, duration of CHF, dyspnea on exertion, fatigue, angina pectoris, mitral regurgitation (on auscultation), tachycardia (more than 120 beats/min), radiographic signs of lung congestion, left ventricular end-diastolic diameter, fractional left ventricular shortening, left atrial size, bundle-branch block on ECG, atrial fibrillation, and ejection fraction.

The 9 risk factors that had been shown to be independent predictors of disease progression within their categories were then reanalyzed using an additional regression model. The following parameters were found to be independent contributors to the progression of CHF to class IV: (1) NYHA Class III; (2) left ventricular end-systolic diameter >51 mm; (3) need for loop diuretics; (4) age over 60 years; and (5) cardiothoracic ratio >50%. Sedentary lifestyle, nocturia, neck vein distension, and pulmonary rales were not independent from these 5 parameters.

**TABLE I** Determinants of Progression of Congestive Heart Failure

| Risk Factor | Patients with Progression (%) | Odds Ratio | P Level (Fisher's exact test, 2-sided) |
|---|---|---|---|
| Age >60 years | 24.2 | 2.52 | 0.0457 |
| ≤60 years | 11.3 | | |
| NYHA class III | 41.5 | 5.38 | 0.0001 |
| NYHA class I/II | 11.6 | | |
| Lifestyle | | | |
| Inactive | 29.3 | 2.87 | 0.0114 |
| Active | 12.6 | | |
| Loop diuretics | | | |
| Needed | 26.3 | 2.44 | 0.0302 |
| Not needed | 12.8 | | |
| Tachycardia >120 beats/min | | | |
| Yes | 36.4 | 2.95 | 0.0376 |
| No | 16.2 | | |
| Cardiothoracic ratio: | | | |
| >50 | 22.7 | 5.42 | 0.0168 |
| ≤50 | 5.1 | | |
| Pulmonary congestion on chest radiograph | | | |
| Yes | 25.0 | 2.75 | 0.0284 |
| No | 10.8 | | |
| Echocardiographic left ventricular end-diastolic diameter (mm) | | | |
| >65 | 30.4 | 3.26 | 0.0010 |
| ≤65 | 11.8 | | |
| Echocardiographic left ventricular end-systolic diameter (mm) | | | |
| >51 | 30.2 | 3.95 | 0.0051 |
| ≤51 | 9.9 | | |
| Fractional shortening (on echocardiography) | | | |
| ≤19 | 29.2 | 3.07 | 0.0191 |
| >19 | 11.8 | | |
| Paroxysmal dyspnea | | | |
| Yes | 28.6 | 2.93 | 0.0091 |
| No | 12.0 | | |
| Neck vein distention | | | |
| Yes | 34.2 | 3.09 | 0.0093 |
| No | 14.4 | | |
| Pulmonary rales | | | |
| Yes | 28.1 | 2.57 | 0.0248 |
| No | 13.2 | | |



| end point | Captopril | Placebo | P |
|---|---|---|---|
| death due to pump failure | 4 | 11 | 0.10 |
| progressive heart failure | 9 | 23 | 0.01 |
| ■ | 11 | 10 | n.s. |

**FIGURE 1. End points in the Munich Mild Heart Failure Trial (MHFT). n.s. = difference not significant.**

Next, discriminant analysis was performed to determine how accurately patients could be classified using these 5 independent risk factors. As shown in Table II, 77.9% could be characterized correctly. The larger the number of independent risk factors present, the higher the risk for progression of CHF (Table III). In the absence of any of

**TABLE II** Accuracy of Independent Risk Factors* in Assigning a Patient to Two Categories (Progression or No Progression of Congestive Heart Failure)

| | Prognosticated Progression by Discriminant Analysis | | | | |
|---|---|---|---|---|---|
| | Yes | | No | | |
| CHF Status During Trial | No. | % | No. | % | Total |
| Progression | 17 | 73.9 | 6 | 26.1 | 23 |
| No progression | 21 | 21.2 | 78 | 78.8 | 99 |
| Total | 38 | 31.1 | 84 | 68.9 | 122 |

*See text for explanation.
CHF = Congestive heart failure.

**TABLE III** Progression of Congestive Heart Failure as a Function of the Number of Risk Factors*

| | Progression of CHF | | | |
|---|---|---|---|---|
| No. of Risk Factors Present | Yes (n = 32) | | No (n = 138) | |
| | No. | % | No. | % |
| 0 | — | — | 12 | 100 |
| 1 | 3 | 11.1 | 24 | 88.9 |
| 2 | 3 | 5.3 | 54 | 94.7 |
| 3 | 12 | 25.5 | 35 | 74.5 |
| 4 | 8 | 42.1 | 11 | 57.9 |
| 5 | 6 | 75.0 | 2 | 25.0 |

*Risk factors are NYHA class III, left ventricular end-systolic diameter (LVESD) > 51 mm, need for loop diuretics, age > 60 years, and cardiothoracic ratio > 50%.
CHF = congestive heart failure.

**TABLE IV** Progression of Congestive Heart Failure as a Function of Risk Factors*—Odds Ratio

| | Progression of CHF (n) | | | p Level |
|---|---|---|---|---|
| No. risk factors | Yes | No | Odds Ratio | (Fisher's exact test, 2-sided) |
| 0–2 | 6 | 90 | 8.13 | 0.001 |
| 3–5 | 26 | 48 | | |

Risk factors are NYHA class III, left ventricular end-systolic diameter (LVESD) > 51 mm, need for loop diuretics, age > 60 years, and cardiothoracic ratio > 50%.

these risk factors, patients did not show progressive heart failure, whereas over 40% of patients with ≥4 risk factors developed progressive CHF. When >2 risk factors were present, the relative risk for the progression of heart failure was 8-fold increased compared with ≤2 risk factors (Table IV).

*Influence of prerandomization variables on the efficacy of captopril:* The same analyses were used to compare results observed in the patients in the placebo and captopril groups. A remarkable difference was found in terms of the effectiveness of captopril in preventing the progression of CHF. As shown in Table V, captopril was more efficacious in the patients who were less severely ill than in those with more severe forms of disease. This difference was most prominent in parameters that reflected congestion, i.e., the need for loop diuretics, the presence or absence of neck vein distension and pulmonary rales, and lifestyle. The influence of disease severity on therapeutic efficacy is again illustrated by analyses of the 5 *independent* risk factors. If ≤2 of these 5 major risk factors for progression of CHF are present, the likelihood of progression of CHF in patients treated with captopril was reduced to less than 5% compared with patients treated with placebo, whereas in the presence of >2 of these risk factors, the relative risk was reduced to one half as a result of captopril therapy (Table VI).

**TABLE V** Relative Risk of Progression of Congestive Heart Failure in Captopril Versus Placebo-Treated Group

| Patient Characteristics | Odds Ratio | P Level |
|---|---|---|
| Age <60 years | 0.39 | NS |
| Age >60 years | 0.27 | 0.0103 |
| NYHA class I/II | 0.12 | 0.0023 |
| NYHA class III | 0.83 | NS |
| LVESD ≤51 mm | 0.40 | NS |
| LVESD >51 mm | 0.39 | NS |
| No need for loop diuretics | 0.08 | 0.0076 |
| Need for loop diuretics | 0.57 | NS |
| Cardiothoracic ratio ≤50 | 0.08 | NS |
| Cardiothoracic ratio >50 | 0.41 | 0.0567 |
| Active lifestyle | 0.01 | 0.0001 |
| Inactive lifestyle | 1.08 | NS |
| No nocturia | 0.49 | NS |
| Nocturia | 0.31 | 0.0159 |
| No neck vein distention | 0.27 | 0.0236 |
| Neck vein distention | 0.67 | NS |
| No pulmonary rales | 0.13 | 0.0037 |
| Pulmonary rales | 0.69 | NS |
| Total | 0.34* | 0.0108 |

*The 95% confidence limits are 0.17–0.68.
LVESD = left ventricular end-systolic diameter; NS = difference not significant; NYHA = New York Heart Association.

**TABLE VI** Progression of Congestive Heart Failure as a Function of Influence of Treatment in the Presence of Few (≤2) or More (3–5) Risk Factors

| Treatment | No Risk Factors | Patients with Progression (%) | Odds Ratio | p Level |
|---|---|---|---|---|
| Placebo | 0–2 | 13.3 | 0.03 | 0.0088 |
| Captopril | 0–2 | 0.0 | | |
| Placebo | 3–5 | 40.5 | 0.57 | NS |
| Captopril | 3–5 | 28.1 | | |

## DISCUSSION

This study was based on two assumptions: (1) Disease progression is a major determinant of prognosis in CHF and can be recognized reliably by clinical signs; and (2) ACE inhibitor therapy retards the progression of CHF and thus improves prognosis. Patients with CHF have an unfavorable prognosis. In mild heart failure, 3- to 5-year mortality is approximately 50%,[4,8] whereas in severe heart failure, 50–70% of patients die within 12 months.[2,3,5,16]

Several parameters have been shown to be predictors of outcome, including neurohormonal, hemodynamic, and clinical criteria.[17] Exercise capacity and left ventricular ejection fraction have been shown to be particularly useful parameters,[18,19] as have activity of the renin–angiotensin system[20] and of the sympathetic nervous system.[21,22] Serum sodium concentration[3,23] and the reciprocal of the atrial natriuretic peptide concentration[24] closely correlate with longevity in CHF. However, these parameters have been of limited value as predictors of prognosis in individual patients, and have thus far not been used as surrogates for mortality in clinical trials designed to improve prognosis.

Therefore, we used a more complex parameter as evidence of progression of CHF: the development of NYHA functional class IV during optimally adjusted therapy. Although assignment to classes I–III is heavily influenced by subjective judgment, the designation of class IV must meet rather rigid criteria. Influenced by both ventricular function and neurohormonal activity, class IV has been associated with a dramatically worse prognosis than have NYHA functional classes I, II, and III.[6,7,17,25] This was confirmed by our results: mortality was 2.5 times higher in patients reaching the end point NYHA functional class IV than in the other patients (53% vs 20%). Therefore, there is good evidence that this end point (class IV) reflects not only the severity of symptoms, but also indicates prognostic deterioration.

Captopril markedly influenced progression of CHF: the number of patients who reached the NYHA functional class IV end point was reduced considerably, the odds ratio being 0.34. This means that treatment with the ACE inhibitor (in conjunction with standard therapy) reduced the likelihood of clinically overt progression of heart failure to one third that seen with standard therapy alone. However, the effect of captopril on disease progression was not reflected in total mortality in this trial. The major reason for this discrepancy can easily be explained by the study design: Switching to active therapy all patients who reached the NYHA class IV end point (and were thus at higher risk) obscured the effects on mortality. In addition, reducing one cause of early mortality in patients with a variety of diseases does not necessarily improve longevity, as has been shown with other therapeutic interventions.[26]

To help define appropriate candidates for captopril therapy of CHF, we investigated the prerandomization variables that affect the likelihood of CHF progression. Since progressive heart failure in itself was a good predictor of mortality in our trial, we were not surprised to find parameters as risk factors for progression of CHF similar to those shown to be major prognostic parameters: systolic function,[18,19] lung congestion,[16,17] exercise capacity[18] (reflected in our study by the NYHA functional classification), and age. This similarity of risk factors for progression of CHF and mortality underlines the important contribution of progression of CHF to the unfavorable prognosis of this condition.

Because patients with more moderate rather than mild forms of CHF are at a higher risk for progressive heart failure, treatment of these patients with ACE inhibitors might be favored. However, the therapeutic effects are not necessarily most prominent in the subgroup at highest risk. On the contrary, our data demonstrated that the milder the disease, the more effective the ACE inhibitor therapy. This was reflected in almost all parameters, NYHA functional class as well as radiographically determined heart size, lifestyle activity, and signs of systemic and pulmonary congestion. It is further confirmed by other trials. Although therapy in this trial reduced the relative risk of progression of heart failure to 34%, the relative risk of mortality in the ACE inhibitor arm in more severely ill patients in the CONSENSUS[2] and Veterans Administration[8] studies were 55 and 81%, respectively. Thus, although the risks of progression of CHF and of death depend on the severity of heart failure, ACE inhibition is more effective in mild heart failure than in moderate or severe heart failure.

We conclude that even patients with relatively mild heart failure are at high risk of progression of their disease and that ACE inhibition favorably influences the natural course of this disease by slowing this progression. The milder the clinical severity of heart failure, the more pronounced the effects of these agents. These data strongly support the inclusion of ACE inhibitors in the therapeutic regimen of patients with mild heart failure.

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# Ventricular Enlargement Following Infarction Is a Modifiable Process

Marc A. Pfeffer, MD, PhD, and Eugene Braunwald, MD

**The dilation and distortion of the left ventricle that may occur as a consequence of myocardial infarction are associated with a heightened risk for adverse cardiovascular events. Infarcts that are extensive, transmural, and involve the apex as well as persistently occluded, infarct-related coronary arteries are predisposing factors for ventricular enlargement. Infarct expansion is an early component of the overall process of volume enlargement, which later continues as a volume overload hypertrophy of the remaining myocardium. Therapy to limit myocardial necrosis has been associated with the preservation of a more normal ventricular architecture. The late phase of ventricular remodeling has also been shown to be amenable to therapy, as chronic administration of angiotensin-converting enzyme (ACE) inhibitors has been associated with a reduction in the extent of ventricular dilation. There is currently a great deal of clinical investigative interest not only in whether ACE inhibition therapy following acute myocardial infarction will result in preservation of ventricular volume and topography, but, more importantly, whether it will lead to an improvement in clinical outcome.**

**(Am J Cardiol 1991;68:127D–131D)**

The cellular necrosis produced by myocardial infarction results in a regional impairment of systolic function. In the case of small infarcts, compensatory responses of the viable myocardium are sufficient to offset the loss of myocytes and maintain global ventricular performance and geometry. However, with more extensive infarction, the ventricular chamber may remodel by an increase in volume that is not the consequence of an increase in distending pressure. This ventricular remodeling following myocardial infarction often is associated with a distortion of the chamber contour and an unfavorable increase in the chamber volume-to-mass ratio.

Infarct expansion, as reviewed in this symposium,[1] is a process in which the infarct region thins and elongates[2,3] and which may be viewed as an early phase of the more global process of ventricular remodeling following infarction. The combination of the loss of myocytes and the early topographic changes in ventricular architecture due to infarct expansion results in an augmented load on the remaining viable myocardium. Although the process of ventricular enlargement following myocardial infarction begins with regional necrosis and infarct expansion, further distortion and enlargement of the ventricular cavity may continue well after histologic healing of the infarcted region.[4] The increased cavitary volume may feed into a vicious cycle whereby enlargement, which initially restores pump function, now increases wall stress and leads to further enlargement. Detailed morphologic studies reviewed in this symposium[5] support the hypothesis that the augmented stress on the remainder of the viable myocardium results in eccentric hypertrophy, which continues well after the healing of the initial myocardial infarction.

The early studies of sequential echocardiography that first identified and defined the clinical process of infarct expansion also demonstrated that patients with infarcts who manifested these changes in ventricular topography were at greater risk for adverse events than those with more preserved ventricular topography.[3,6] Volume en-

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largement following myocardial infarction has been shown to be a powerful predictor of reduced survival, with even relatively small increases in volume being associated with a heightened relative risk of death.[7] The volume of the infarcted left ventricle has been shown to be related to the extent of myocardial damage, as assessed by the percentage of the ventricular silhouette that is either akinetic or dyskinetic.[8,9] In addition, other factors such as the degree of transmurality, the patency of the infarct-related vessel, and the location of the noncontractile tissue have an important influence on ventricular enlargement.[10]

The enlargement, or remodeling, of the infarcted left ventricle is, however, subject to modification. Of course, the prevention of myocardial infarction, by definition, would eliminate the risk of volume enlargement and so the importance of primary prevention measures must be underscored. Once an acute myocardial infarction begins to evolve, measures to restore and maintain the coronary artery patent are of proven benefit for salvaging myocytes, preserving contractile function, and, most importantly, reducing mortality[11,12] (Figure 1 [a]). The pooled experience of those placebo-controlled trials that evaluated the efficacy of thrombolytic therapy revealed only a modest improvement of ejection fraction (54% for active therapy vs 51% for placebo), which, although significant, would not be anticipated to explain the 20% improvement in survival associated with this form of therapy.[13] These observations and the demonstrated efficacy of late thrombolytic therapy in prolonging survival, even when administered beyond the presumed period of myocyte salvage, have led to the expansion of the simple paradigm in which the reduction of infarct size results in an improvement in ventricular function and leads directly to an improvement in survival.[14,15] The modification of ventricular enlargement following myocardial infarction is emerging as an important process that may account not only for the favorable late actions of thrombolytic therapy (Figure 1 [b]), but as well for the benefits of nitrate and angiotensin-converting enzyme (ACE) inhibition (Figure 1 [d]).

Thrombolytic therapy in acute myocardial infarction has been associated with a reduction of ventricular enlargement that is more impressive than the actual improvement in ejection fraction.[16,17] Thrombolytic therapy is anticipated to limit myocardial necrosis and transmurality, and thereby limit ventricular remodeling (Figure 1 [a]). However, as reviewed in this symposium,[18] the observation that patients with patent infarcted-related vessels are less likely to undergo late ventricular enlargement indicates that sustained coronary perfusion may also reduce the late phase of ventricular remodeling (Figure 1 [b]).

The modification of hemodynamic factors associated with an augmented myocardial wall stress provides another promising modality with which to attenuate ventricular remodeling following infarction. As reviewed in this symposium,[19] the judicious use of nitroglycerin in the acute phase of the infarct was associated with myocardial salvage and an improved clinical outcome (Figure 1 [c]). ACE inhibition therapy has been studied extensively in an animal model and has been consistently effective in attenuating the late phase of ventricular enlargement (Figure 1 [d]).[20] These animal studies, reviewed in this symposium,[21,22] have demonstrated that the reduction of ventricular volume with chronic ACE inhibition is a consequence of both the attenuation of structural remodeling and the reduction in distending pressure. In the experimental model of myocardial infarction, this pharmacologically-induced attenuation of ventricular remod-

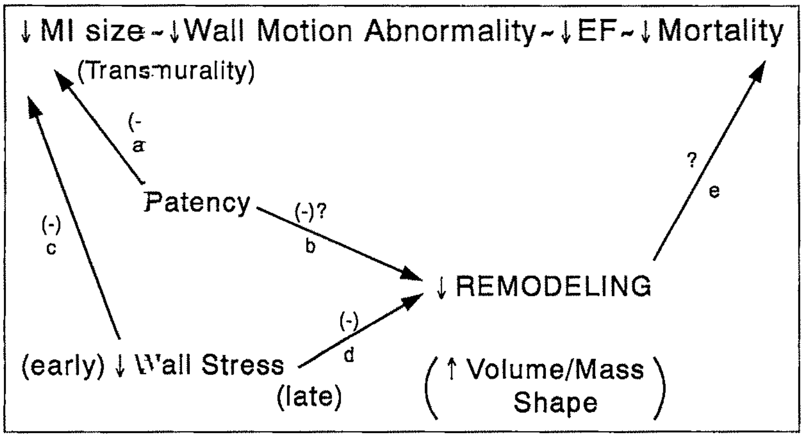

**FIGURE 1. Relation between myocardial infarct (MI) size, ventricular function (ejection fraction [EF]), and mortality and the interaction with therapy modifying post-MI ventricular remodeling. (a) Early restoration of infarct vessel patency salvages myocytes, limits transmurality and improves outcome (supply). (b) Maintenance of patency beyond the period of myocyte salvage has been associated with less remodeling. (c) Early optimization of hemodynamics salvages myocytes (demand), limits transmurality and requires outcome. (d) Angiotensin-converting enzyme inhibition therapy beyond the period of myocyte salvage reduces ventricular remodeling. (e) Will therapy that reduces ventricular remodeling lead to improved survival?**

eling was associated with an improvement in survival.[23]

Clinical studies of the use of ACE inhibition following myocardial infarction have consistently shown that, in selected patients, the process of ventricular enlargement following infarction can be attenuated (Figure 1 [d]). In a study of the survivors of a first anterior Q-wave infarction, substantial left ventricular enlargement was shown to have already occurred within the first 3 weeks.[24] With that abnormal baseline volume, patients were randomized to receive either placebo or captopril in addition to conventional therapy and were followed for 1 year. The objective of this trial was to determine whether a late phase of ventricular enlargement occurred in humans and, if so, whether this process could be attenuated by chronic therapy with ACE inhibition. Using a sensitive paired *t* analysis, progressive enlargement was observed in the placebo group, but not in the patients assigned to active therapy. This late volume enlargement in the placebo group was heterogeneous, with some patients showing marked enlargement and others exhibiting a preservation of ventricular size and shape in the year following infarction. More extensive baseline akinesis and dyskinesis and the lack of patency of the infarct-related vessel emerged as important descriptors for the heightened likelihood of manifesting late-phase ventricular enlargement. When compared with placebo patients at similar risk, patients at high risk for ventricular enlargement who were assigned to captopril therapy exhibited an attenuation in ventricular enlargement.[24]

In survivors of inferior as well as anterior Q-wave infarctions, Sharpe and coworkers[25] performed serial quantitative echocardiographic assessments of ventricular size. From their baseline volumes at 8 days, patients assigned to placebo had further ventricular enlargement and a deterioration of performance. Randomization to furosemide therapy did not alter this process of ventricular enlargement in the year following infarction; however, captopril therapy was associated with a reduction in ventricular size and an improvement in function. Both of the aforementioned studies, which used cardiac catheterization and echocardiographic techniques to measure volume, have demonstrated that captopril can be safely administered to survivors of Q-wave infarctions with left ventricular dysfunction and that chronic therapy with this agent was associated with a preservation of ventricular size and function.[24,25]

These observations have bolstered the investigational interest in the use of ACE inhibition following infarction. Recent studies have focused on the earlier administration of ACE inhibitors in acute myocardial infarction in an effort to modify the acute process of infarct expansion as well as the late phase of ventricular enlargement. This early initiation of an ACE inhibitor requires an even closer scrutiny of safety issues since the attendant risk of precipitating ischemia is increased in the acute phase. As reviewed in this symposium,[26,27] 2 trials employing ACE inhibitors indicate that this therapy can be well tolerated when administered to selected patients within the first 24 hours of myocardial infarction.

An interesting recent approach has been to combine thrombolytic therapy with prompt ACE inhibition therapy during the hyperacute phase of infarction.[28,29] Despite an initial report of unacceptable hypotension with a combination of streptokinase and intravenous captopril,[28] more recent work has provided promising information that oral captopril can be administered as an adjuvant therapy to a thrombolytic agent. Both the Captopril and Thrombolysis Study Trial (CATS), combining captopril and streptokinase (presented in this symposium[26]), and the Captopril plus tPA following Acute Myocardial Infarction (CAPTIN) trial, determining the effects of tissue plasminogen activator and captopril (LeJemtel, TH, Hochman JS, Sonnenblick EH: Personal communication), are adding the ACE inhibitor as early as possible to thrombolytic therapy, within the first 6 hours of myocardial infarction. These studies have quantitative echocardiographic end points as primary outcome variables and should provide definitive information as to whether adjutant therapy with captopril can augment the effects of thrombolytic therapy in attenuating ventricular remodeling (Figure 1 [b,d]).

Studies of the early administration of ACE inhibition are not limited to patients deemed suitable for thrombolytic therapy. As presented in this symposium,[27] the safety pilot trial of open-label zofenopril therapy (part of the Survival of Myocardial Infarction Long-term Evaluation [SMILE] trial) within the first 24 hours of acute myocardial infarction in patients who did not receive thrombolytic therapy has generated information that early therapy is generally well-tolerated. This report confirms the overall safety of ACE inhibitors in acute myocardial infarction and provides some promise that larger trials may demonstrate a clinical efficacy. Despite promising observations and new approaches, the clinical efficacy of ACE inhibition therapy following myocardial infarction re-

**TABLE I** Ongoing Multicenter Randomized Trials of Safety and Efficacy of Angiotensin-Converting Enzyme Inhibition Therapy in Improving Clinical Outcome of Myocardial Infarction*

|  | No. | ACE | Patients | Initiation (days) | Follow-up (months) |
|---|---|---|---|---|---|
| SAVE | 2,231 | Cap | EF ≤40% | 3–16 | 42 |
| AIRE | 2,000 | Ram | CHF | 3–10 | 6 |
| SMILE | 3,000 | Zofen | All | 1 | 1.5 |
| Chinese Card. | 10,000 | Cap | All | 1.5 | 1 |
| CONSENSUS II | 9,000 | Enal | All | 1 | 6 |
| ISIS-4 | 40,000 | Cap | All | 1 | 1.2 |
| GISSI-III pilot | 1,000 | Lisin | All | 1 | 1.5 |

*Ongoing multicenter randomized trials with clinical end points of angiotensin converting enzyme inhibitor therapy.

ACE: angiotensin converting enzyme; AIRE: Cap = captopril; Card. = ; CONSENSUS = Co-operative North Scandinavian Enalapril Survival Study; Enal = enalapril; GISSI-III = Gruppo Italiano per lo Studio Selks Streptochinasi nell'Infarto Miocardico; ISIS-4 = Fourth International Study on Infarct Survival; Lisin = lisinopril; Ram = ramipril; SAVE = Survival and Ventricular Enlargement; SMILE = Survival of Myocardial Infarction Long-term Evaluation; Zofen = Zofenopril.

mains to be demonstrated (Figure 1 [e]). Studies whose end point is ventricular topography (Figure 1 [b,d]) can only imply a clinical benefit, which then must be convincingly demonstrated before ACE inhibition therapy is added to the armamentarium of postinfarction management. Large trials with sufficient power to detect an improvement in clinical end points will be required to ascertain whether this attenuation in ventricular remodeling will be translated into an improved clinical outcome (Figure 1 [e]).

At present, there is a major international investigative effort that is focused on defining the clinical impact of ACE inhibition following a myocardial infarction. The Survival and Ventricular Enlargement (SAVE) trial was the first such major undertaking which commenced randomization in 1987 and will continue blinded observation until early in 1992. This cooperative venture between 45 centers in Canada and the United States was designed to determine whether captopril therapy would prolong survival and reduce the proportion of patients who experienced a marked deterioration of ejection fraction in the years following myocardial infarction. As detailed in this symposium,[30] the SAVE investigators have targeted patients with a depressed left ventricular ejection fraction to determine the long-term consequences of ACE inhibition therapy. More recently designed studies are, in general, studying a broader population and are initiating ACE inhibition therapy in the early phase of infarction (Table I).

The current intense effort to evaluate the potential for ACE inhibition therapy to improve clinical outcome following infarction should soon provide a detailed evaluation of its role in patients experiencing a myocardial infarction. Together, these studies should define fully the overall efficacy of ACE inhibition therapy in reducing adverse clinical outcomes such as mortality, the development of heart failure, recurrent nonfatal myocardial infarction, and other significant cardiovascular events. These detailed studies should also fully characterize the risk of ACE inhibition therapy in the postinfarct patient, since taken cumulatively, thousands of patient-years of exposure to ACE inhibition therapy will be available for direct comparison with patients assigned to placebo. Importantly, this major focus on the use of ACE inhibition postinfarction should also provide insight of a mechanistic nature regarding the progression to and prevention of symptomatic heart failure in survivors of myocardial infarction. New information should also be generated regarding the potential interactions between neurohumoral influences, the progression of coronary disease, and electrical stability with ventricular size and shape, and therefore a further expansion of the postinfarction paradigm will be necessitated.

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